American Heart Journal

VOL. 29 JANUARY, 1945 No. 1

Original Communications

THE NEUROVASCULAR SYNDROME PRODUCED BY HYPERABDUCTION OF THE ARMS

THE IMMEDIATE CHANGES PRODUCED IN 150 NORMAL CONTROLS, AND THE EFFECTS ON SOME PERSONS OF PROLONGED HYPERABDUCTION OF THE ARMS, AS IN SLEEPING, AND IN CERTAIN OCCUPATIONS

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INTERMITTENTLY over a period of many years, attention has been focused on vascular and neurologic syndromes resulting from anatomic anomalies in the neck and shoulder girdle.

The earlier reports[1-11] emphasized for the most part the basic conception that extensions of the transverse processes and cervical ribs arising from the seventh, sixth, or, rarely, the fifth cervical vertebra, may be responsible for pressure on the subclavian artery, the brachial plexus, or both, which, in turn, may result in paresthesias, coldness, impaired circulation, and, in severe cases, gangrene of the fingers. Roentgenograms of the cervical area demonstrate the presence of these bony anomalies in true cases, but it was later observed that this combination of symptoms and signs may develop in the absence of bony abnormalities. Dissection in such cases demonstrated several anatomic patterns, the most common of which are: (a) A tendinous or cartilaginous band extending from, or in the place of, a rudimentary cervical rib and acting in the same manner as its bony counterpart.[16] (b) Abnormal torsion and pinching of the subclavian artery and the brachial plexus as they pass between the anterior and the medial and minimal scalenus muscles above their points of attachment to the first rib.[12-16] (c) An arrangement which permits unusual ease of compression of the subclavian vessels and brachial plexus between the clavicle and the first rib, especially upon backward and downward bracing of the shoulders.[5, 17]

Any of these anatomic patterns may be present without producing symptoms, but may under certain conditions produce the syndrome which has been too loosely classified as the "scalenus anticus syndrome."

Presented before the 17th Annual Meeting of the Central Society for Clinical Research, Chicago, Nov. 3, 1944.
Received for publication Dec. 4, 1944.

TABLE I

DIFFERENTIAL DIAGNOSIS OF CERTAIN NEUROVASCULAR SYNDROMES OF THE UPPER EXTREMITIES

	CERVICAL RIB SYNDROME	SCALENUS ANTICUS SYNDROME	RUPTURED NUCLEUS PULPOSUS OF THE CERVICAL SPINE	COSTOCLAVICULAR COMPRESSION BY BACKWARD AND DOWNWARD BRACING OF THE SHOULDERS (FALCONER AND WEDDELL)	SYNDROME PRODUCED BY HYPERABDUCTION OF THE ARMS
AGE	Common in early middle life or later	Same	Reported cases mostly in young adults, probably any age	Any	Only young adults have been studied
SEX	Both	Both	Both	Both	Both
SYMPTOMS	Paresthesias, numbness, pain in fingers and hand (ulnar distribution most common)	Same, tenderness over scalenus area	Intermittent symptoms; paresthesias, numbness, anesthesias, pain in fingers and hand, pain and tenderness over area of ruptured cervical disc	Paresthesias, numbness, pain in fingers and hand	Paresthesias, numbness, pain in fingers and hand
SIGNS	Cyanosis in adduction of hand, occasional hyperhydrosis	Same	Not striking	Cold, blue hands, tendency to chilblains and "Raynaud's attacks"	Normal color in adduction Pallor on hyperabduction in some cases
GANGRENE	In extreme cases, dry Moderately painful	Same	Never occurs	Arterial thrombosis with gangrene in severe cases	In extreme cases, dry Moderately painful
POSITION AGGRAVATING SYNDROME	Adduction with tension, as in lifting weight	Same, plus turning head away from affected side	Extension of neck, straining, coughing	Backward and downward bracing of shoulders; hyperextension of neck	Hyperabduction of arms
OBLITERATION OF PULSE	Arms in extreme adduction or/and with head turning away from affected side	Same, incidence less common than formerly believed	Never	60 to 70 per cent of normals	Arms in various positions of hyperabduction; 85 to 90 per cent normals

OSCILLOMETRIC READINGS	Confirmatory	Confirmatory	Normal	Confirmatory	Confirmatory
SURFACE TEMPERATURE OF FINGERS AND HAND	Cool in adduction	Same	Normal	Cool if prolonged in aggravating position	Cool in hyperabduction
EVIDENCE OF VENOUS OBSTRUCTION	None	None	None	Pronounced dilation of superficial arm and pectoral veins, especially in infrared photographs	Not pronounced except with primary axillary venous thrombosis. Further study needed
ROENTGENOGRAMS	Cervical ribs unless only rudimentary fibrous bands exist	Negative	Cervical spine: narrow intervertebral spaces *late.* Intraspinous air or radiopaque substances may demonstrate defect in spinal canal	Angle exposures may show asymmetrical thoracic inlet, with evidence of narrowed space in aggravating postures	Negative
VENOGRAMS	Rare, or no abnormalities	Obstruction only if vein is pinched closed on adduction, or turning of head	Normal	Obstruction in some cases Further study indicated	Obstruction only if vein is pinched off on hyperabduction, with or without thrombosis (total experience too limited for final conclusions)
LOCAL ANESTHETIC	No value	If successful, temporary relief	No value	No value	Further studies needed
TREATMENT	Temporary relief in hyperabduction Surgical: excision	Relief on hyperabduction Surgical: severing scalenus anticus muscle	1. Traction, immobilization 2. Surgical procedures: (a) removal of disc, (b) fixation	1. Mild cases, exercises for improvement of postural tone of muscles of shoulder girdle 2. Severe cases, removal of segment of offending rib	Relief in adduction: Avoiding posture of hyperabduction

Patients often complain of paresthesias, numbness, and tingling after sleeping or working with their arms in the position of hyperabduction.* Most frequently they change their positions and little attention is paid to these phenomena. Few studies have mentioned the subject. Todd[18] reported an experiment on himself in which he slept with his right arm stretched out almost vertically under his head. This was continued with some interruptions for eight years (1913 to 1921), at which time tingling, loss of sensation, swelling, desquamation, causalgia, and paronychia developed within three months, and affected especially the right thumb and index finger. He stated that the experiment failed to bring forward evidence relating to vascular changes, although the studies reported do not appear very complete in that regard. The syndrome disappeared when he ceased to sleep in this posture. No thorough study of the incidence of these phenomena in normal persons, or of the precise mechanism responsible for it, was made.

During the past five years the author has encountered, in several instances, evidence of marked vascular and neurologic changes produced by prolonged "hyperabduction" of the arms. In this paper, case his-

Injection of a 1 per cent solution of procaine in the region of the scalenus anticus muscle failed to prevent the obliteration of the pulse by the above-mentioned maneuvers, although the procedure was subject to the inevitable factors of uncertainty in this area. Roentgenologic studies of the right shoulder girdle, chest, and cervical spine showed nothing abnormal.

The mechanisms involved in the symptomatology and the obliteration of the pulse in this case were obviously more complex than in the others, and will be considered later in this paper.

Fig. 1.—Sleeping position frequently seen in hospital wards, in which obliteration of the pulse and overstretching of the nerve trunks may occur.

COMMENTS

In each of the first five cases, the syndrome had previously been misinterpreted. The following possibilities had been considered: Raynaud's syndrome, thromboangiitis obliterans, intrinsic or extrinsic tumor of the cervical cord, ruptured nucleus pulposus in the cervical area, infectious polyneuritis, ulnar and median nerve injury, cervical rib, and scalenus anticus syndrome.

This gave rise to the following questions:

1. What is the incidence of obstruction of the major arteries to the upper extremities as a result of hyperabducting the arms in various positions?
2. Is this abnormal or normal?

shoulder joint. Thereafter he had pain deep in the shoulder joint which made it impossible for him to raise his arm from his side. He recalled pain in the anterior axillary fold, but this was not the site of major discomfort. He was asymptomatic after three weeks. About six weeks after the original injury he again suffered similar pain and disability after hitting an opponent while boxing. The pain in the anterior axillary fold was a more striking feature this time. A lump the size of his fist developed in the scapular region on the posterior surface of the shoulder. This slowly subsided, but, after the second injury, he continued to feel as if his shoulder and upper arm were "going to sleep," and constantly experienced a sensation of heaviness in the region of his shoulder. During the preceding month this condition had grown progressively worse. He had noted increased numbness along the ulnar side of the forearm and hand, involving the fourth and fifth fingers.

For years prior to his accidents this patient had frequently slept with his hands under his head as a pillow. He had experienced paresthesias, but not to a serious degree. About two weeks after his second injury he slept in this position and was unable to move his right arm upon awakening. It was necessary to lift it with his left hand, and it was several hours before he could use it.

Physical Examination.—The patient was a stocky, heavily muscled, 27-year-old man. There were no significant abnormalities unrelated to the problem under discussion. The blood pressure in the right arm was 128/66, and in the left arm, 128/68.

Inspection revealed no abnormalities. There was no engorgement of the collateral veins of the right shoulder. With the arm in a dependent position the skin was of normal color, texture, and temperature as compared with the left upper extremity. When, however, the arms were hyperabducted, the right hand blanched and later flushed, whereas the left hand retained a normal color. There was no limitation of motion of the shoulder, elbow, or wrist joints. No crepitus could be felt in the right shoulder. Measurements revealed that the arms were essentially equal in size.

Testing the upper extremities for sensation to pin prick revealed a variable pattern of decreased sensation on the right side over the posterior aspect of the shoulder, the lateral side of the arm, the ulnar side of the forearm and hand, and the entire fifth finger and ulnar side of the fourth finger. The deep reflexes were normal bilaterally.

The right radial and brachial pulses were obliterated by the following procedures:

1. Abducting the arm laterally 45 degrees.
2. Abducting the arm anterolaterally to a 90-degree angle.
3. Abducting the arm posterolaterally to a 45-degree angle.
4. Abducting the arm in any of the above directions to just below the level where the pulse was obliterated, and then having the patient rotate his head to the left.
5. By having the patient contract his right pectoralis major and minor muscle group with the arm in any position.
6. By having the patient inspire deeply and hold his breath.
7. By having the patient force his shoulders backward and downward.

Elevation of the shoulder or contraction of shoulder muscles other than the pectoralis group would not result in obliteration of the pulse.

By contrast, the pulse in the left arm could be obliterated only by having the patient hyperabduct his arm above a 150-degree angle, or by having him force his shoulders backward and downward.

could be achieved); (3) the position at which it first disappeared as the arm was hyperabducted; (4) whether deep inspiration could produce obstruction with the arm held in a marginal position (i.e., one in which slight movement would open or shut off the arteries); (5) whether the incidence of this sign was influenced by muscular development; (6) whether neurologic symptoms could be produced within two minutes

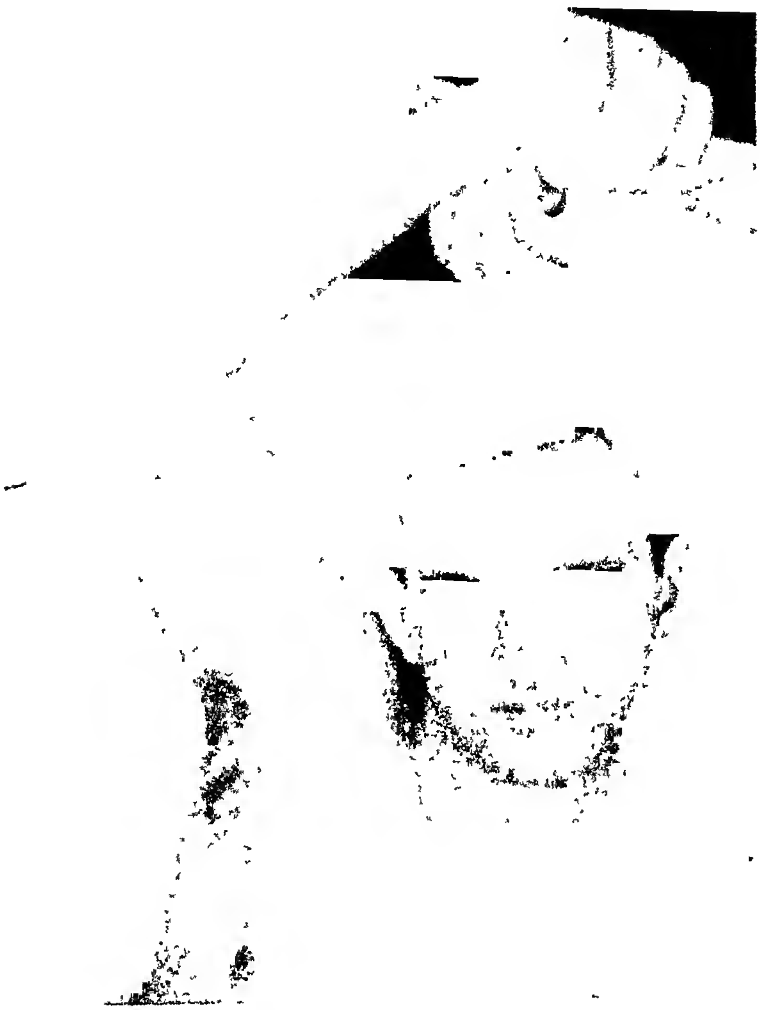

Fig. 3.—Second position for test. In many instances the pulse is completely obliterated by simply hyperabducting the arm to this or a *similar position* (1 plus or 2 plus difficulty). In others, it is more difficult to ascertain an exact position at which the pulse disappears (2 plus or 4 plus difficulty). In the third group the pulse cannot be obliterated in any position.

without interference with the major circulation, as evidenced by absence of change in the pulse. Questionable observations were checked by more than one examiner.

The results of this study were as follows:

In one hundred twenty-five of one hundred fifty "normal" subjects (83.3 per cent), obliteration of the right arm pulse could be produced by hyperabduction of the right arm above the head (Fig. 3). In one

3. What is the mechanism by which this syndrome is produced?

4. What percentage of persons recognize symptoms which arise from assuming this position and tend to protect themselves against it?

5. Can sensory changes be produced by assuming this position in the absence of obliteration of the arterial pulsation?

Studies were undertaken to answer these and additional questions.

STUDIES ON NORMAL ADULTS

One hundred fifty young adults, considered to be normal with regard to this syndrome, were examined with the cooperation of Lieutenant Colonel Austin B. Chinn and Major Roscoe Millet. Observations were made as follows:

Fig. 2.—Patient in position for test. Arm abducted anteriorly and laterally. The pulse is strong and is easily felt in this position.

The patient was seated in a small, straight-backed chair. The radial pulse was checked for its presence and strength in positions below shoulder level (Fig. 2). Each arm, in turn, was hyperabducted with the examiner's fingers on the radial pulse (Fig. 3). Subjects whose vessels were obstructed easily were, in fifteen instances, checked by having them lie in bed and hyperabduct their arms (Fig. 4). Notations were made as to (1) whether the pulse could be obliterated in any position; (2) whether this was easy or difficult to accomplish (in other words, whether there were many points or only one point at which this

TABLE II

RESULTS OF A STUDY OF OBLITERATION OF THE PULSES IN THE MAJOR ARTERIES OF THE ARMS OF 150 NORMAL SUBJECTS PRODUCED BY HYPERABDUCTION OF THE ARMS

DIFFICULTY	RIGHT ARM		LEFT ARM	
	NUMBER OBLITERATED	PERCENTAGE	NUMBER OBLITERATED	PERCENTAGE
1 plus	49	32	48	32
2 plus	45	30	47	31
3 plus	23	15	22	14
4 plus	8	5	7	4
Total	125	83	124	82

was *easily* produced by hyperabduction of the corresponding arm, as described. In only eleven of the one hundred fifty subjects (7.4 per cent) could no obliteration be produced in either arm. Neurologic symptoms, including paresthesias, were produced in two cases (in one in the left, and in one in the right) within two minutes, in the *absence* of obliteration of the pulse.

The frequency of obliteration of the pulse was much higher than anticipated, and the facts certainly warrant the conclusion that the anatomic arrangement is a normal one (in that it occurs in a very high percentage of persons) which, under specific conditions, may produce a specific syndrome. This is important because this position of hyperabduction is today being widely, but erroneously, used as a test for the scalenus anticus syndrome. The scaleni are relaxed rather than tensed in this position. As was pointed out by Ochsner, Gage, and DeBakey,[15] this position frequently relieves the pain in the scalenus anticus syndrome.

Observations were made as to whether there was any correlation between the degree of muscular development and the ease with which the pulse could be obliterated. No such correlation could be established, except that obliteration of the pulse was very difficult, and frequently impossible, to produce by this method in the "loose jointed" type of person.

Eight subjects could block their pulses by muscular contraction in the marginal position (the position in which a slight movement of the arm would obliterate or restore the pulse). The author has in the past seen numerous persons who could do this in any position by contraction of the pectoralis major and minor group.

In three instances, the pulse could be obliterated in the marginal positions by deep respiration. In two, however, the pulse was definitely made more prominent by deep respiration.

Questioning revealed that thirteen of the one hundred fifty subjects frequently slept with their arms hyperabducted, usually with the elbows somewhat flexed. Six of these slept comfortably in this position. In these, obliteration could be produced only with difficulty, and not in the position in which they usually slept. Seven frequently fell asleep with their arms hyperabducted in similar positions, but soon developed suf-

hundred twenty-four of the one hundred fifty (82 per cent) "normal" persons, obliteration of the left arm pulse could be produced by hyperabduction of the left arm above the head. Obliteration of the radial pulse paralleled that of the brachial pulse.

There was considerable variation in the difficulty encountered in producing this obliteration. In some instances it could be produced by merely hyperabducting the arm, and sometimes occurred before the arm reached 180 degrees. In others, it was necessary to apply moderate stress to the arm, forcing it posteriorly and moving it about into different positions in order to find one at which the pulse was obliterated.

Fig. 4.—Third position for test. If obliteration occurs in second position, a check is made to ascertain whether the pulse is absent in the position in which patient usually sleeps. This may be modified by using other positions under suspicion, such as those used in overhead occupations, e.g., painting ceilings, riveting, etc.

These variations in difficulty were graded as 1 to 4 plus, i.e., 1 plus was easy, and 4 plus was difficult, but possible. The results are given in Table II.

It will be noted that in 94, or 62 per cent, obliteration of the right arm pulse, and in 95, or 63 per cent, obliteration of the left arm pulse

ment of transition into the axillary artery and vein) and the main trunks of the brachial plexus pass posterior to the pectoralis minor, just beneath the coracoid process (Fig. 7). They are well protected in adduction (Fig. 5), but when the arm is hyperabducted they are stretched around and underneath the coracoid process. By the same action the pectoralis minor is drawn tight (Figs. 6 and 7). This double action results in different degrees of stretching and pinching of the artery, vein, and nerves in different persons. Another point where pressure and torsion may be produced by certain positions of the arms and shoulders is found where the artery, vein, and plexus pass between the clavicle and

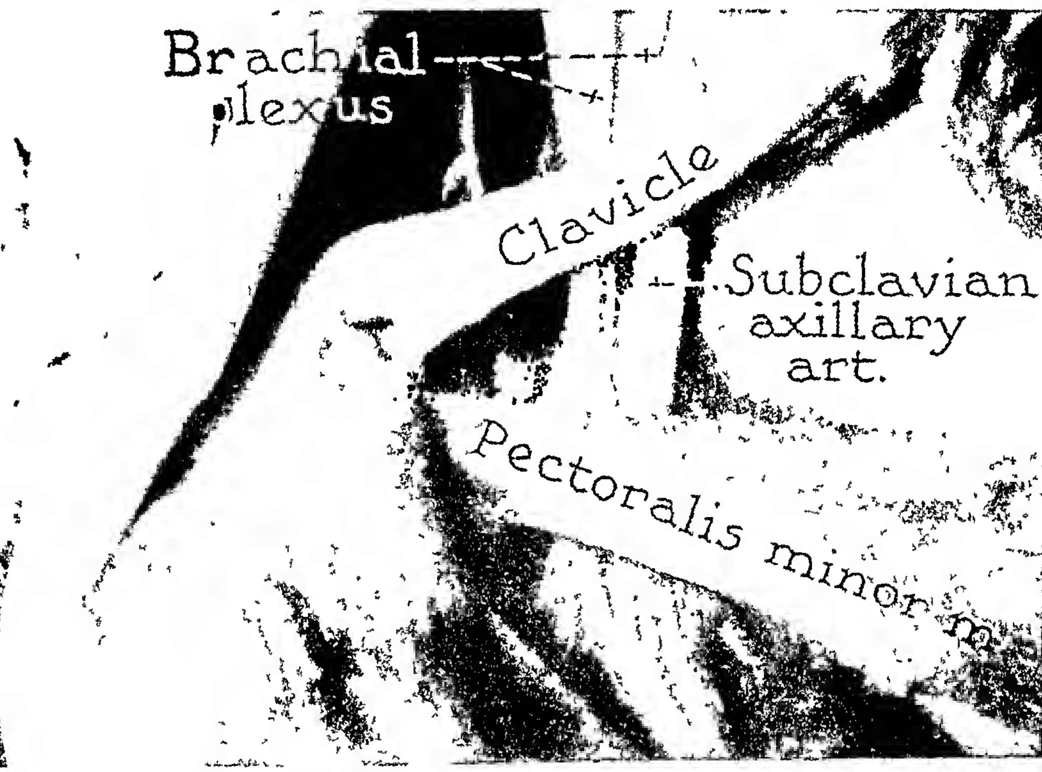

Fig. 5.—Photograph showing relations of brachial plexus and subclavian-axillary artery with the arm in a position of relaxed abduction. They are under no tension or pressure.

the first rib (Fig. 6). Eden[20] described a case (Case 3) with a normal first rib in which obliteration of the pulse occurred as a result of this mechanism when the arm was abducted. Although his patient had severe symptoms, there is no definite history of prolonged maintenance of this posture, either at work or asleep. This was further admirably described by Falconer and Weddell[17] in reference to a syndrome produced by having the patients force their shoulders backward and downward, or by hyperextension of the neck. These movements result in pinching of the vessels and the plexus between the anterior surface of the first rib and the posterior surface of the clavicle. They demonstrated that this pinching, which may result in obliteration of the pulse and

ficient discomfort to bring their arms down below shoulder level. In six of these subjects, obliteration of the pulses was easy to accomplish, and occurred in the sleeping position which produced the symptoms. One developed numbness in the right hand when tested by this procedure, without obliteration of the pulse.

It has since been noted that, in certain instances, the pulse may be present intermittently. In a position which at first produces obstruction, the pulse may suddenly become strong—to remain, or to disappear as suddenly. It has also been noted that the position of the head may sometimes affect the obliteration of the pulse. Turning the head toward, or away from, the arm being tested may open or close the subclavian-axillary artery. In this group the scalenus muscles may play an important part. Although the direction in which it is necessary to turn the head to produce obliteration is usually constant for one subject, it varies with different persons, e.g., in some, obliteration is produced by turning the head toward the arm being tested, in others by turning the head away from this arm. Flexing the head and neck reduces the incidence of obliteration. Hyperextending increases the incidence. This will be discussed later in this paper. Exact statistical data on the occurrence of these phenomena, which were observed more recently, are not available.

A CONSIDERATION OF THE ANATOMIC MECHANISM WHICH PRODUCES THIS SYNDROME

The frequency with which obliteration of the pulse and neurologic symptoms could be produced in the series of "normal" subjects indicates that the mechanism cannot be based on a structural abnormality, such as a cervical rib or the scalenus anticus syndrome.

The pathologic changes must result from prolonged occlusion of the arterial supply and damage to the nerve trunks caused by stretching, pinching, prolonged ischemia, or all three. Pathologic changes are relatively uncommon because (1) only a small portion of the population sleep or work with their arms hyperabducted for long periods of tim (as in painting a ceiling); (2) most of these will change their position by bringing their arms down below shoulder level when discomfort develops; and (3) in many the arteries are obstructed or the nerves stretched excessively only in certain specific positions, so that, ordinarily, because of frequent changes in posture, the patients do not develop the syndrome even while they sleep with their arms hyperabducted.

The present knowledge of this phenomenon permits only preliminary deductions regarding mechanisms involved.

A review of the anatomic arrangement, with dissections, reveals that there may be variations in the mechanisms responsible for this syndrome in different persons, and even in the same person, as the arms change position. Two points of torsion, stretching, and pinching, operating either alone or jointly, appear to play the major roles in most cases. One is the point at which the subclavian artery and vein (at the seg-

the obliteration of the pulses of the normal subjects in our series whose pulses could be obliterated only with difficulty, and with backward pressure, as well as hyperabduction. This appeared to play an important role in Case 5, in which the pulse disappeared on both sides after backward and downward movement of the shoulders. The subcoracoid-pectoralis minor syndrome appeared to play a major role in the obliteration of the pulse caused by hyperabduction, for it occurred when the arm was abducted anterolaterally to 90 degrees, a position in

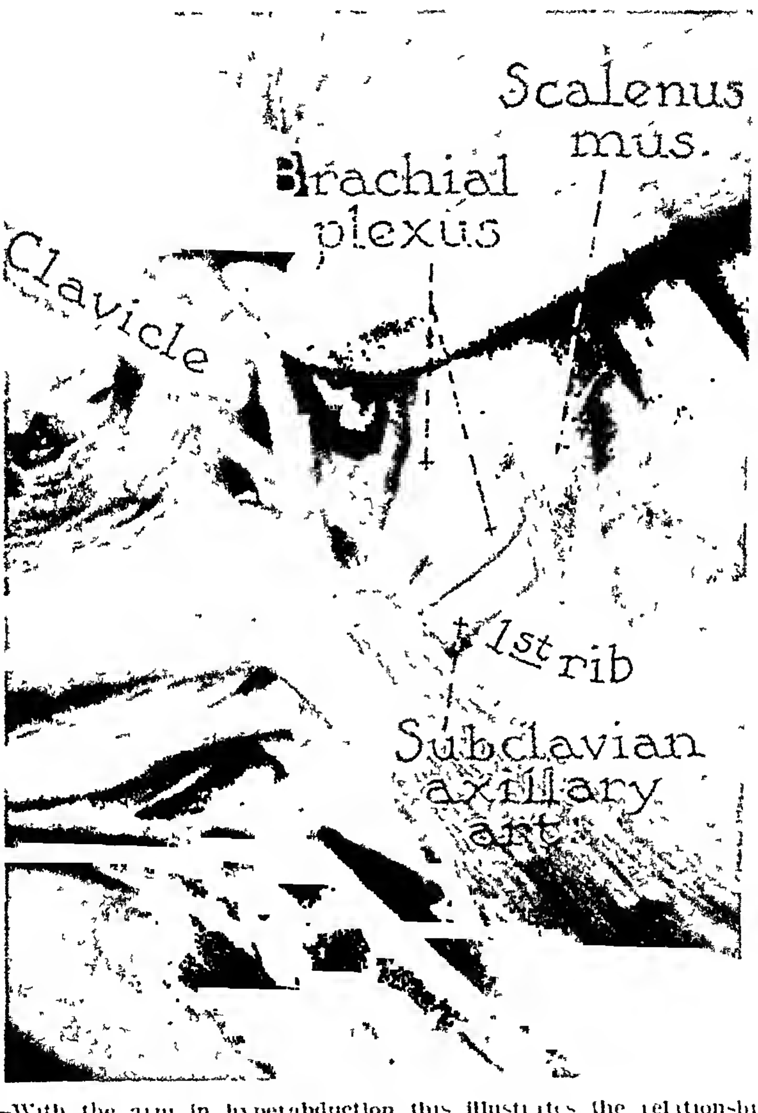

Fig. 7.—With the arm in hyperabduction this illustrates the relationship of the brachial plexus and subclavian-axillary artery to the first rib, coracoid process, anterior scalenus muscle, and pectoralis minor muscle. The clavicle has been lifted out of position.

which the costoclavicular space is at a wide phase. The reason for the pronounced aggravation of this syndrome in the right arm after the injuries must await solution, if and when the area is explored surgically.

Other anatomic stresses and pressures in this extremely complex portion of the body may play some part in this phenomenon in certain

sensory neurologic symptoms, is also a normal, or at least a very common, phenomenon, for it could be produced in twenty-five of fifty men, and thirty of fifty women. In severe cases, relief could be achieved only by preventing the pinching by means of an appropriate surgical procedure.

In studying the syndrome produced by hyperabduction, it has been found that, in certain positions and in certain instances, costoclavicular compression of the subclavian vessels and plexus plays an important role. Through the cooperation of Major Sylvan Moolten, it has been

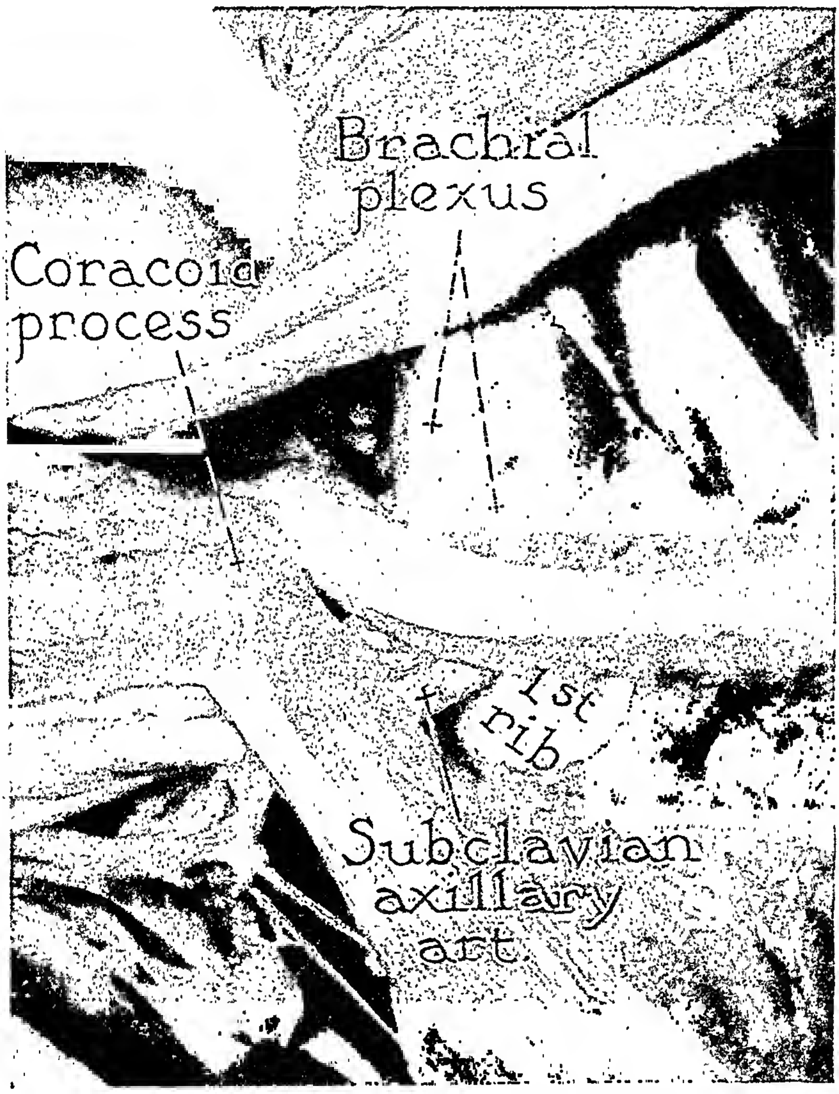

Fig. 6.—Photograph showing relations of brachial plexus and subclavian-axillary artery with the arm in hyperabduction. In many instances in this position the vessels and nerves are stretched and subject to torsion as they pass beneath the coracoid process and behind the pectoralis minor muscle. Marked torsion and pinching may also take place between the clavicle and the first rib.

clearly demonstrated that, under these conditions, there may be a marked reduction in the width of the space between the clavicle and the first rib. The brachial plexus can be seen to become twisted and flattened out into its component cords by this pressure; at the same time, the subclavian artery is pushed downward and forward, and is compressed (Fig. 6). This mechanism may have played a major part in

it after horizontal bar exercises or prolonged hyperabduction of the arms while doing up the hair. Venographic studies will doubtless be of interest. These are contemplated.

SUMMARY AND CONCLUSIONS

1. A neurovascular syndrome which is produced by hyperabduction of the arms is described.

2. This is capable of producing gangrene secondary to occlusion of the subclavian artery, and neurologic sensory complaints probably secondary to stretching, and ischemia of the brachial plexus trunks.

3. There are two zones of stretching, torsion, and pinching which contribute to the production of this syndrome: (a) the point at which the axillary-subclavian vessels and the trunks of the brachial plexus pass posterior to the pectoralis minor muscle and beneath the coracoid process; and (b) the point at which the subclavian vessels and the trunks of the plexus pass between the clavicle and the first rib.

4. Further anatomic and functional studies of these and other mechanisms which may contribute to the production of this syndrome will be highly desirable.

5. The first four patients reported herein developed their syndromes as a result of prolonged sleeping in the supine position with their arms hyperabducted; in each case this resulted in arterial occlusion or stretching of the involved nerve trunks. In Case 5 the symptoms were aggravated by a double injury involving the right shoulder. In additional cases, to be reported later, the syndrome has developed as a result of occupational hyperabduction.

6. Data are presented to demonstrate that occlusion of the subclavian artery by hyperabduction of the arms is a normal phenomenon. Most persons will avoid prolonged hyperabduction because of the symptoms produced.

7. It is recommended that persons whose pulses can be occluded in the hyperabducted position refrain from sleeping or working with their arms in that position.

8. It is also recommended that special attention be paid to the state of the pulse and complaints of paresthesias and numbness from patients whose arms are in hyperabduction on operating tables or in splints or casts, in order to avoid the neurovascular complications which occasionally occur as a result of neglect of this principle.

9. This report is published in the belief that calling attention to this syndrome will lead to correct diagnoses in the future, so that patients may be advised regarding the proper treatment for the majority, namely, sleeping with the arms in safe positions, or, in cases of occupational hyperabduction, changing occupations.

10. In a few cases in which the costoclavicular syndrome is dominant, surgical treatment may be necessary.

instances. Some of these have been well described by Wartenberg[22] in his discussion of "Brachialgia Statica Paresthetica," or nocturnal arm dysesthesias, which occur independent of hyperabduction.

The stretching or pinching of the nerve trunks probably produces the immediate paresthesias. Ischemia due to impaired blood supply to the nerves may play a part after prolonged hyperabduction. Violent hyperabduction can, as is well recognized, produce paralysis by severe stretching or tearing of some of the brachial plexus trunks.

In addition to the difference in structural relationships, the wide range in reactions to the same positions may depend in part on the great variation in rate of impairment of nerve conduction which follows compression of short segments of peripheral nerve. In view of the studies of Denny-Brown and Brenner,[21] we have attributed this to uneven pressure gradients in the nerve bundles, with consequent variation in the degree of ischemia because of the escape of some small vessels. It is thought that such a relationship is an expression of corresponding relative degrees of ischemia, and not a direct consequence of pressure on nerve fibers.

The fact that tingling and numbness began peripherally and progressed centrally in our cases is in agreement with the principle of centripetal paralysis as observed and formulated by Lewis, Pickering, and Rothschild.[23] They found that the sensations of cold and heat, and also muscular power, were subject to the same laws of centripetal paralysis after the production of ischemia by the use of a blood pressure cuff. The numbness which develops in the finger tips is not due to a process in the finger tips themselves, but rather to changes in those portions of the nerves that lead to the finger tips and which have been rendered ischemic. In their experiments, the amount of blood leakage was distinctly less than in our cases, in which only the subclavian axillary vessels are occluded, and the many collateral vessels of the shoulder may function fairly freely. The nerves of the brachial plexus are nevertheless subject to stretching and pinching, and are therefore at least locally subject to ischemia. The ulnar trunk in the axillary area, since it is the lowest one, is the most vulnerable to damage by stretching of this order, and this corresponds with the occurrence of paresthesias in the ulnar distribution in some of our cases.

The local gangrene of the tissues at the finger tips in Case 1 was, in our belief, the result of prolonged ischemia. It is thought that some blood must leak through the main vessels either continuously or intermittently, for otherwise massive thrombosis would probably occur. Collateral vessels must have contributed to the nutrition of the extremities in all of the cases reported.

Although none of the patients herein reported suffered from primary axillary venous thrombosis, it is possible that the same mechanism may have been responsible for its occurrence in patients who have developed

MOMENTARY ATRIAL ELECTRICAL AXES

II. Atrial Flutter, Atrial Fibrillation, and Paroxysmal Tachycardia

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WE HAVE long been interested in the supposedly unusual combination of paroxysmal atrial tachycardia and atrioventricular block, and have recently directed attention to the unexpected frequency with *which block occurs during paroxysms.*[1] *We were also impressed with* the fact that these same patients showed, relatively often, closely associated attacks of atrial flutter or fibrillation.[2] Several patients showed all three types of atrial mechanism disturbance in the course of a few hours or days. This logically led us and others[3] to suppose that the fundamental mechanisms of these three disturbances might be closely related. The present report describes an effort to justify such an inference by clinical experiment.

Barker, Wilson, and Johnston,[4] reporting similar observations, have been led to similar conclusions. Their data led them rationally to the conclusion that paroxysmal atrial tachycardia is the result of a circus rhythm in the atria, the path of which passes through one of the specialized atrial nodes. That this might be true appears to have been suggested first by Iliesen and Sebastiani;[7] more recently, Ashman and Hull[8] have accepted this explanation for some cases, at least, of paroxysmal tachycardia.

The recent paper of Barker, Wilson, and Johnston[4] contains a summary of the available evidence bearing on the point, and it must be confessed that from this evidence one may reasonably conclude that paroxysmal tachycardia may be due to a circus mechanism. They support their opinion by citing data relating to the electrocardiographic form of the atrial complex, the constancy of the rate and its usual failure to be influenced by exercise, the effect of reflex vagal stimulation, the mode of action of quinidine and digitalis, *the occasional occurrence* of A-V block and of alternation of the P-P cycle length, and the less common close association with atrial flutter or fibrillation.

A circus mechanism might theoretically account quite satisfactorily for most of the known characteristics of paroxysmal tachycardia, as Barker and his associates have indicated. However, actual proof is thus far lacking that such a mechanism does exist. The clinical ex-

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Received for publication Feb. 21, 1944.

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with the Einthoven hypothesis of the values thus derived. Inasmuch as we were able to record only two leads at one time, it was impossible to trace off the three leads as though they were recorded simultaneously, particularly in atrial fibrillation, in which there is no cyclic repetition of the waves. Lewis presented his data schematically in the form of a ring, in which the direction of movement is clockwise when viewed in the sagittal plane, and counterclockwise in the horizontal and frontal planes.

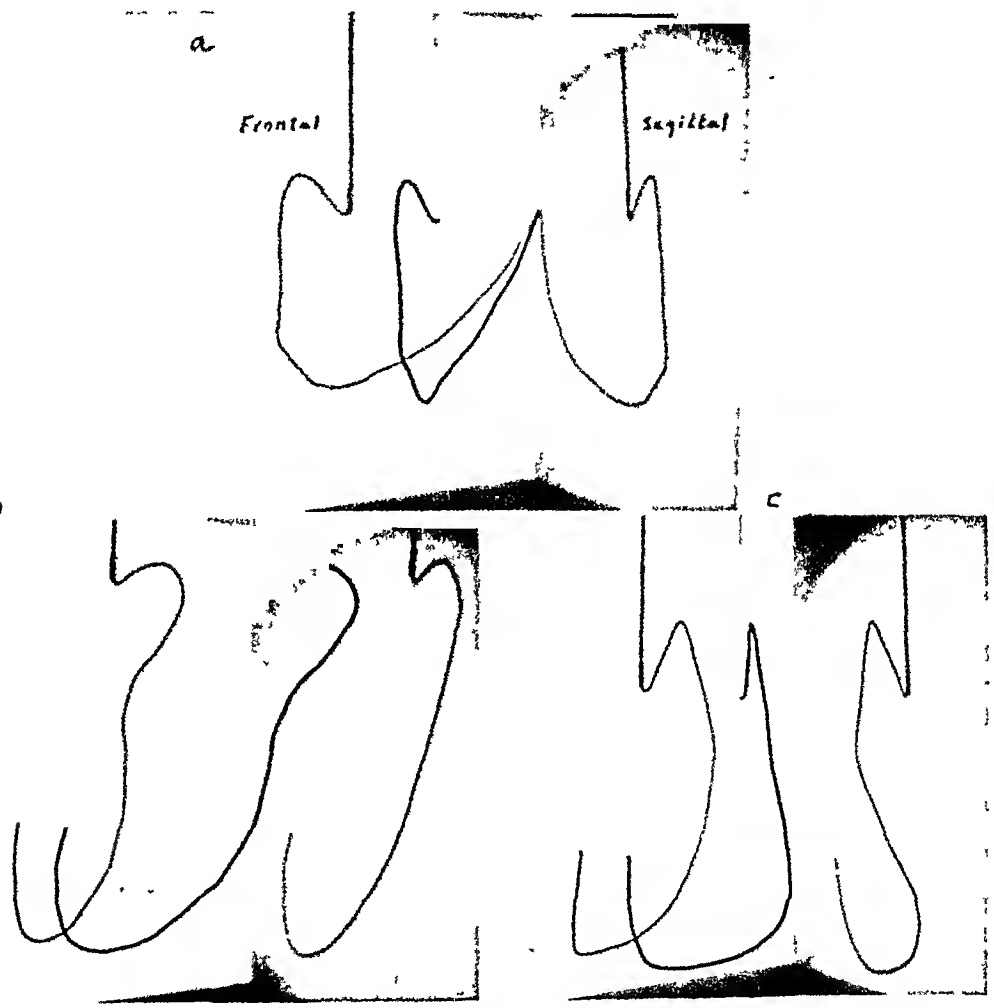

Fig. 1.—*a*, Model constructed from Lewis' data on flutter. *b* and *c*, Our own cases of flutter.

In the first case of our own which is illustrated (J. L., Fig. 1, *b*), the direction of rotation of the axes is clockwise in the sagittal and frontal planes, and counterclockwise in the horizontal plane. In the second case (J. P., Fig. 1, *c*), movement is in a clockwise direction in the frontal plane and counterclockwise in the horizontal plane; the sagittal view, however, shows an S-shaped contour. In the two other cases that we have studied the curves closely resemble those shown in the figures.

periments to be described below represent an attempt to put this question to the actual test. We recognize fully the theoretical, as well as the practical, limitations of the method which we have employed. We feel, however, that the results themselves support the validity of the method, at least for the purposes for which we have utilized it.

In a preceding paper[7] we described the use of electrocardiograms taken in three planes on the chest, and the derivation from them of curves and three-dimensional figures representing the momentary directional change of the consecutive atrial electrical axes. It is, in effect, a slight modification of the method originally employed by Lewis, Drury, and Iliescu[8] in their demonstration of the presence of a circus movement in atrial flutter and fibrillation. Our purpose in making this study has been (1) to reproduce the results obtained by Lewis, et al., in cases of flutter and fibrillation, and (2) to subject patients with paroxysmal tachycardia to the same type of clinical study. The curves obtained have been compared with those obtained from patients showing sinus rhythm. Some of the data have been briefly discussed elsewhere.[9] Barker, et al.,[4] have pointed out the similarities between paroxysmal tachycardia with A-V block and flutter, and have also indicated the differences. Certainly it is in these cases of tachycardia with A-V block that there is most often an associated flutter or fibrillation.[2] It is also precisely these cases which are most readily studied by Lewis' method as we have employed it, for in them some of the P waves are isolated. and are not superimposed on the preceding QRS-T complexes.

EXPERIMENTAL RESULTS

Atrial Flutter.—Although the disciples of Rothberger[10] adhere to the belief that flutter and fibrillation are the result of rapid stimuli arising from parasystolic foci, there has been wide acceptance of the concept developed extensively by Lewis, viz., that the cause of these disturbances of mechanism is movement of the impulse through a circular pathway, which may be regular or irregular, respectively. On the basis of data from experimental flutter, and from one case of flutter in man, Lewis believed that in the usual cases of clinical flutter the circus movement passed around the mouths of the venae cavae. We have constructed Fig. 1, *a,* from Lewis' data,[8] after plotting the curves in the three planes by the procedure previously outlined. In addition, we have studied four cases of flutter of our own, and illustrate the movement of the momentary electrical axes in two of them in Fig. 1, *b* and *c*.

We adopted Lewis' method of choosing a base line in those cases in which there is continuous electrical activity of the atrium, namely, a line drawn midway through the undulations of the string. Lewis[8] accepted this procedure and demonstrated a satisfactory agreement

momentary electrical axes, at least with the base lines employed, which appears, in agreement with Lewis, to be compatible with the presence of a circus movement in cases of atrial flutter and fibrillation, although of course it does not prove its presence. It now remains to ascertain, by analogous methods, the nature of these curves in paroxysmal tachycardia.

Case 1.—J. P., a white man, aged 67 years, John Sealy Hospital No. 56427, was admitted Dec. 20, 1943. For the preceding four years he had had cardiac asthma; for six months before admission there had been frequent attacks of paroxysmal nocturnal dyspnea. Orthopnea, dependent edema, and oliguria had been present for eight days. The blood pressure was 120/80; numerous asthmatic râles were heard over the entire chest; hepatomegaly, ascites, and marked edema of the legs were noted. The venous pressure was 27 cm. of saline. Twenty-four grains of digitalis leaf were given in the first forty-eight hours. On Dec. 21, 1943, 2 c.c. of mercupurin were injected intravenously, causing a urinary output of 6,100 cubic centimeters. On December 22, the electrocardiogram showed paroxysmal atrial tachycardia, with partial A-V block; the atrial rate varied from 154 to 200 per minute. At 4:30 that afternoon atrial flutter was present (*Fig. 1, c*). Tachycardia had recurred the next morning, December 23; during the day 13 grains of quinidine were given, and, on December 24, sinus rhythm was present. The tachycardia recurred on December 27; quinidine failed to interrupt the disturbance, and the patient died December 30.

The electrocardiographic data on this patient are summarized in Fig. 3, showing those obtained during the paroxysmal tachycardia on December 23, and contrasting them with those of the sinus rhythm on December 24. These data include, in order from above downwards, a strip from a limb lead; strips from Leads I and III in each plane of the chest leads; the curve of the momentary electrical axes calculated for each 0.01 second; and, lastly, a photograph of a three-dimensional model combining the curves for the three planes, and showing the frontal and sagittal projections. The photographs show, more clearly than a description, the difference in direction and contour between the course of the consecutive atrial axes during tachycardia and during sinus rhythm.

Case 2.—M. M., a white woman, aged 34 years, John Sealy Hospital No. 10902, was admitted Aug. 24, 1943. Rheumatic mitral stenosis had been recognized in 1929, and the diastolic murmur of aortic insufficiency had first appeared in 1940. In spite of frequent periods of complete rest in bed, in the preceding three years she had maintained compensation with difficulty, although she had taken a daily ration of digitalis leaf. During this time she had shown atrial flutter and fibrillation, both of which had been controlled by the use of quinidine. At the time of this admission she manifested the usual signs and symptoms of congestive heart failure. On August 25 sinus rhythm was recorded; on August 27 there was a paroxysm of atrial tachycardia which was terminated by carotid sinus pressure. On September 9 and 10 atrial fibrillation was present; this was replaced spontaneously by tachycardia with 2:1 A-V block on September 12. Quinidine in a dose of 0.6 Gm. was given, and, on September 13, sinus rhythm was found. On September 14, however, flutter was present. From September 25

These examples of the pathway of the consecutive electrical axes in cases of atrial flutter show an individual variation which is not surprising. Any circus movement which is present in such cases might be expected to vary from patient to patient. The axes rotate in a manner compatible with a circus, and in each instance return to the initial direction.

Atrial Fibrillation.—We have analyzed tracings taken in three planes from six patients with atrial fibrillation. Because of the variation from moment to moment of the record of atrial activity, it is obvious that tracings obtained in the three planes, unless taken simultaneously with three instruments, must be tracings that cannot be properly combined into a three-dimensional figure. The curves plotted from the directions of the consecutive atrial axes of some sections often showed beautiful circular contours; curves derived from other segments of the same record might be extremely irregular and bizarre. In some instances one plane might show repeated circles, differing in size and

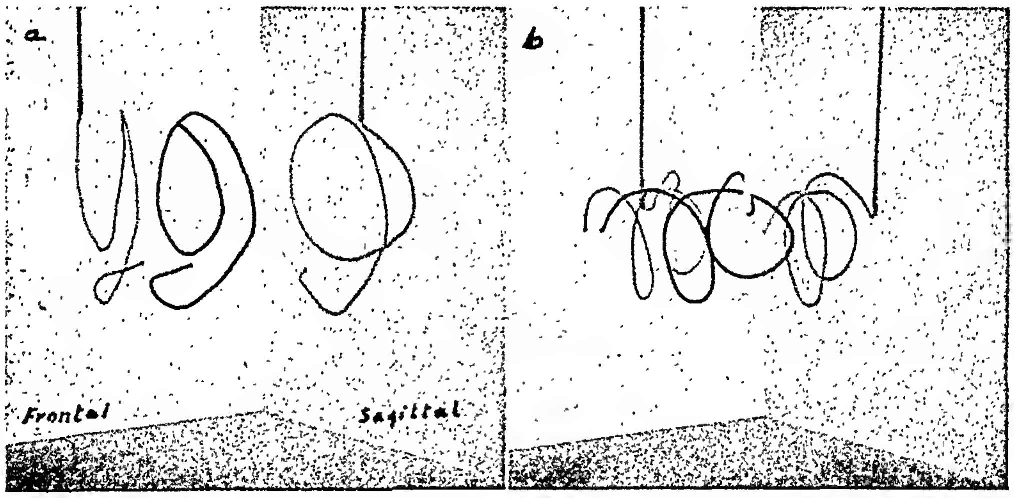

Fig. 2.—*a* and *b*, Atrial fibrillation in two cases of mitral stenosis.

shape, while the other planes failed to show this. Fig. 2, *a*, illustrates this possibility. We have combined the tracings in the sagittal and frontal planes from a patient with mitral stenosis, realizing, of course, that these are not simultaneous tracings in the two planes, but are records of two entirely different impulses, taken at different times. The sagittal shadow shows a variable circus, whereas the frontal shadow is much more irregular and further removed from a circus. Thus an irregular circus movement in the atria may yield projections upon the three planes of recording which show good agreement with, or great deviation from, a circus, depending on the plane in which the electrical forces are recorded, or in which the model is viewed. The same point is borne out by Fig. 2, *b*, constructed from the records of another patient with rheumatic mitral stenosis.

Paroxysmal Tachycardia.—The data just depicted show that this procedure is capable of revealing the serial change in the direction of the

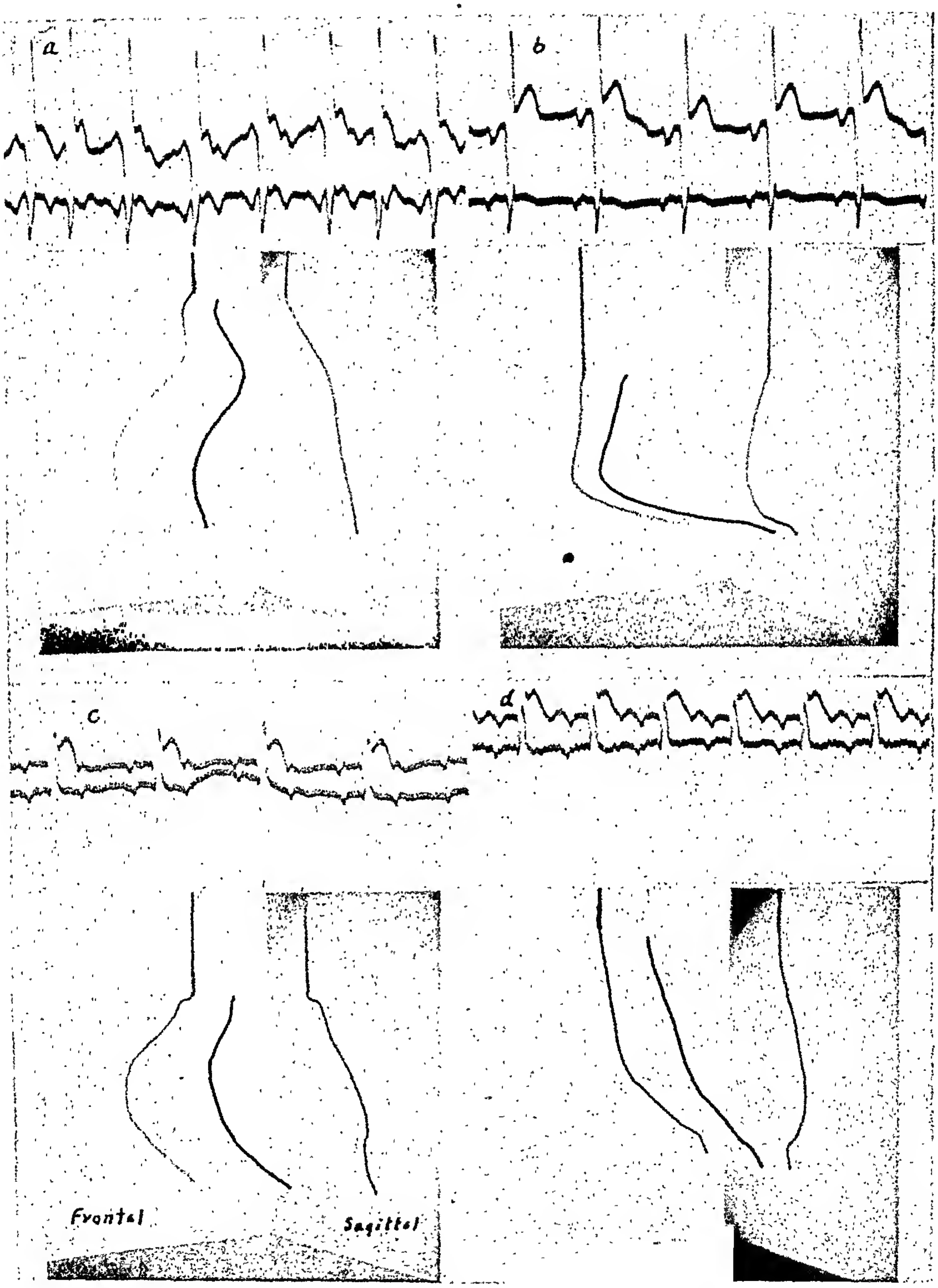

Fig. 4.—*a*, Leads I and III in the frontal plane, and below the model representing the atrial axes, during paroxysmal tachycardia in Case 2. *b*, Same, during sinus rhythm. *c*, Case 3 during paroxysmal tachycardia; see text for position of the electrodes. *d*, Case 3 with sinus rhythm.

through October 4, tachycardia with 2:1 A-V block was present, with the atrial rate at about 200 per minute. This was not controlled by repeated administration of quinidine; additional digitalis, however, given October 6 to 8, converted the mechanism into atrial fibrillation, which was, in turn, converted to sinus rhythm by 2.3 Gm. of quinidine on October 11. Tachycardia recurred October 14; again it was not stopped by quinidine, but was converted on October 28 to sinus rhythm by digitalis. Quinidine in a dose of 0.3 Gm. three times daily maintained the sinus rhythm.

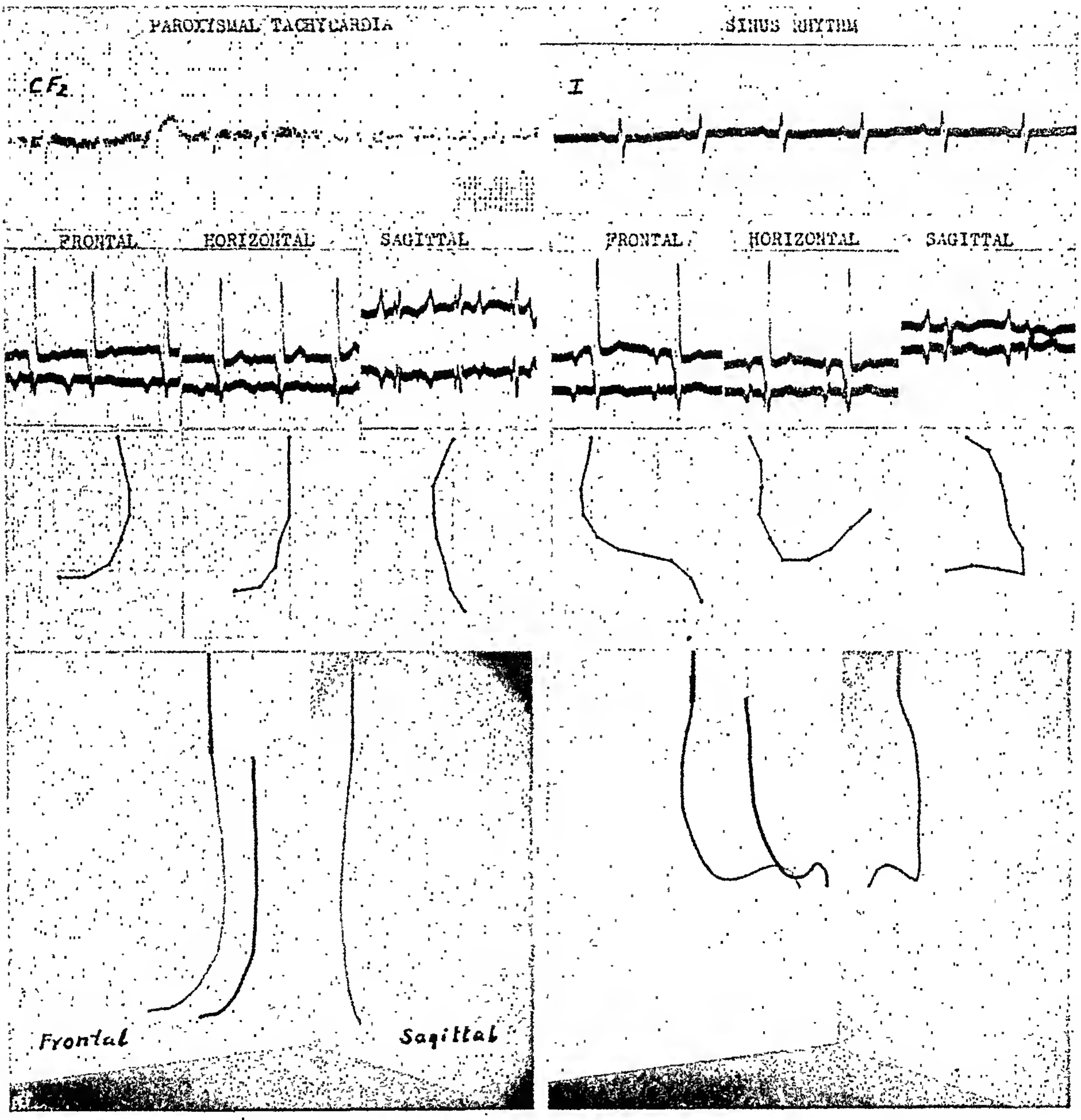

Fig. 3.—Paroxysmal tachycardia compared with sinus rhythm in Case 1. The upper electrocardiograms show the mechanism. The second line contains short pieces from the three planes, as indicated, of Leads I and III, recorded simultaneously. Below them are the consecutive axes for each 0.01 second. The photographs are of models constructed in the manner described in the preceding paper.

Fig. 4, *a*, shows a strip of Leads I and III, taken simultaneously in the frontal plane; below is a model representing the course of the consecutive atrial axes during the attacks of atrial tachycardia. Fig. 4, *b*, gives the same data for a period of sinus rhythm.

limb leads showed slight differences during the tachycardia with block, when compared to those recorded later. Fig. 5, *c* and *d*, shows the frontal plane electrocardiograms and the three-dimensional models for the tachycardia and the sinus rhythm. Although not as marked as those in the other cases, the differences appear definite, and are, we believe, enough to support the clinical conclusion that the tachycardia was probably of ectopic origin.

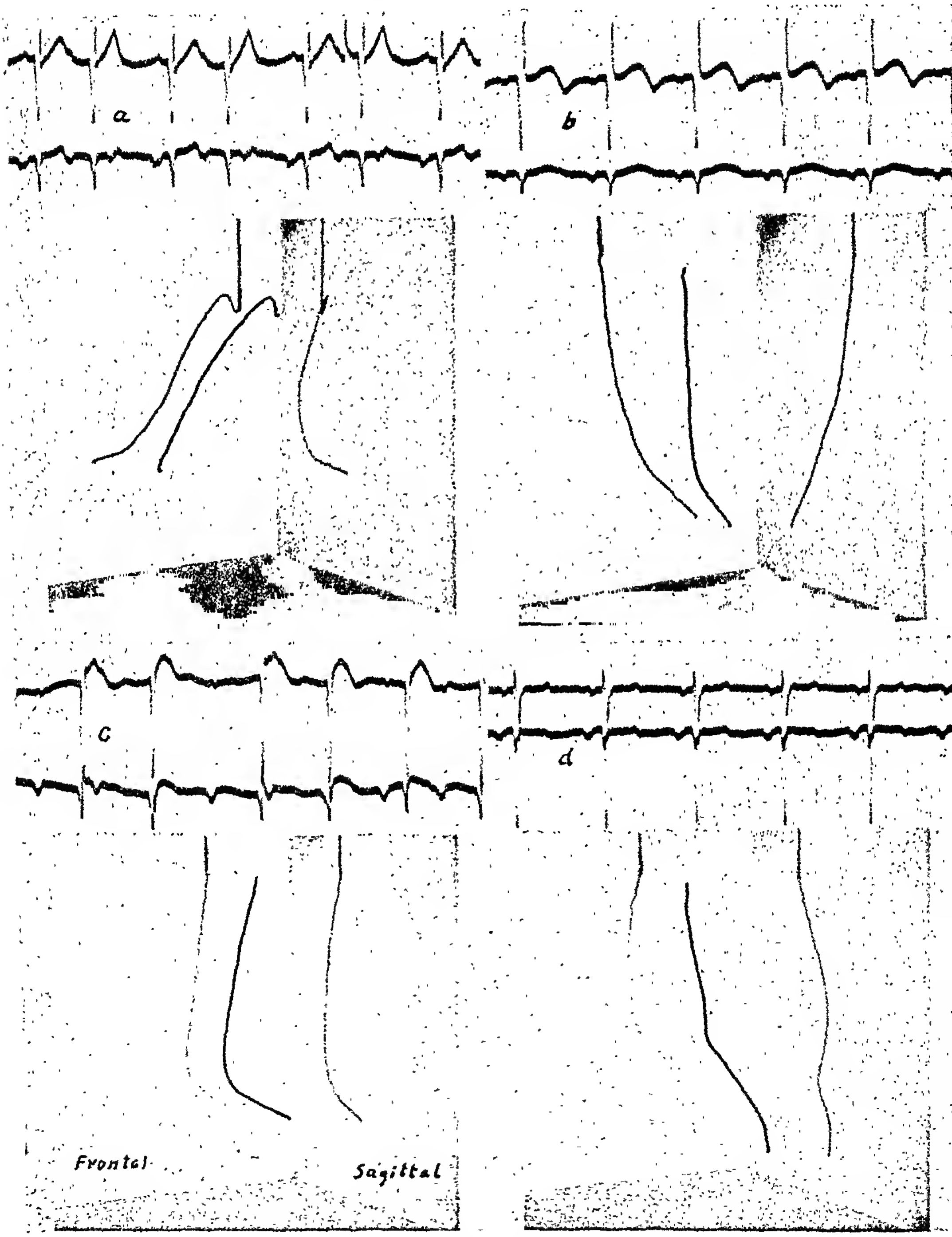

Fig. 5.—Leads I and III from the frontal plane, with model below. *a*, Case 4 during paroxysm, and *b*, during sinus rhythm. *c*, Case 5 during paroxysm, and *d*, during sinus rhythm.

CASE 3.—A. S., a white man, aged 59 years, John Sealy Hospital No. 79775, was first admitted on Jan. 26, 1943. During the ensuing nine months he had three other admissions, and died Oct. 9, 1943. The blood pressure varied little from 200/120; renal insufficiency was present, with chronic uremia. A pericardial friction rub was heard three weeks before death. On Sept. 8, 1943, frequent atrial premature beats were recorded. On September 15 and 16 paroxysmal atrial tachycardia, with 2:1 A-V block, was present; this stopped spontaneously, and subsequent tracings showed sinus rhythm. Necropsy showed a greatly enlarged heart (1,000 grams), fibrinous pericarditis, and marked renal arteriolosclerosis.

Fig. 4, *c* and *d*, compares the tracings in the frontal plane and the atrial axes during tachycardia and sinus rhythm. The tracing in Fig. 4, *c*, was taken with the right arm electrode at the right nipple and the left arm electrode on the left nipple. The triangle thus formed in the frontal plane must be viewed from the back, but, for the model below, correction has been made to conform with the routine positions. The curve in Fig. 4, *d*, was taken with the electrodes properly placed.

CASE 4.—M. J., a Negro woman, aged 62 years, John Sealy Hospital No. 62324, was admitted Jan. 18, 1944. She had been in the hospital in 1939 and 1941, both times with congestive heart failure caused by hypertensive heart disease. Before this admission her physician had given her digitalis leaf in a dose of 0.1 Gm. three times daily for nine days. This had caused some decrease in the edema, but had also caused nausea, vomiting, and diarrhea. Her first electrocardiogram showed atrial tachycardia; the rate varied from 140 to 158 per minute, with aberration and alternation of the QRS complexes, and occasional A-V block with dropped beats. Carotid sinus pressure increased the grade of A-V block. Quinidine was given, and appeared to be responsible for reversion to sinus rhythm on January 21. Although clinically she seemed to be improving, she died suddenly January 23. Necropsy showed cardiac enlargement (680 grams), aortic and coronary arteriosclerosis, renal arteriolosclerosis, and chronic passive congestion.

Fig. 5, *a*, shows the tracing in the frontal plane, and the model derived as previously described, during the tachycardia; Fig. 5, *b*, is from data obtained during sinus rhythm.

CASE 5.—G. H., a Negro woman, aged 53 years, John Sealy Hospital No. 84222, was admitted Nov. 23, 1943. Three weeks before admission she had fainted; a physician found that she had arterial hypertension, and prescribed digitalis tablets, of which she took sixteen in the following week. At that time she saw another physician, who gave her 0.6 Gm. of digitalis three times daily for three days. The exact amount of digitalis that she had taken was not definitely ascertained, but it was obviously too much; this clearly warranted the diagnosis of digitalis intoxication and adequately explained the severe nausea and vomiting which were present on admission. The blood pressure was 170/94; there was no evidence of congestive heart failure. The electrocardiogram on November 24 showed atrial tachycardia; the rate was 125 per minute, with partial A-V block of the Wenckebach type. On November 26, 2:1 A-V block was present. By November 29 sinus rhythm had appeared spontaneously.

From a clinical standpoint this patient was thought to have paroxysmal atrial tachycardia with A-V block of the type which we have observed to result from digitalis overdosage. The P waves in the

largement of the pulmonary conus and the right atrium and ventricle. The electrocardiogram showed right axis deviation and evidence of right ventricular strain. Some observers felt that they could detect the diastolic rumble of mitral stenosis. Digitalis leaf was given in 0.3 Gm. doses for two days, and 0.1 Gm. daily thereafter; a satisfactory loss of edema resulted. On Oct. 16, 1943, paroxysmal tachycardia developed, with an atrial rate of 139 per minute. Three hours later the rate was 146 per minute, and for the following two days stayed at about 150 per minute. Fig. 6, *a*, shows the tracing of Leads I and III in the frontal plane, obtained at the slower rate; fortunately, the P waves may be clearly distinguished at this time, although later curves at the faster rate did not permit this. The patient left the hospital October 21, and no record during sinus rhythm was obtained. He died suddenly at home Nov. 21, 1943.

CASE 7.—P. H., a Negro man, aged 79 years, Out-patient Department No. 41908, had paroxysmal tachycardia with A-V block on Aug. 24, 1943. He had been under observation and treatment for hypertensive heart disease since 1930. After an absence of two years he visited the Clinic Aug. 17, 1943, with marked congestive heart failure. Digitalis leaf in a dose of 0.3 Gm. daily was advised. He returned August 24; on this day the electrocardiogram showed atrial tachycardia with a rate averaging 166 per minute, usually with 2:1 A-V block; the grade of block was greatly increased by carotid sinus pressure. Fig. 6, *b*, shows a strip of Leads I and III in the limb leads and in the frontal plane. This patient was the first one on whom we recorded the chest leads in three planes, and, as in Case 3, we had not yet standardized the position of the electrodes. Their position is such that, as in Case 3, the triangle formed must be viewed from the back. Correction has been made in the model to conform to the other curves taken in what was later found to be the proper method. The curves in the frontal plane were taken with a film speed of 75 mm. per second. This patient refused to enter the hospital, and died a few days later at home.

CASE 8.—E. M., a white man, aged 54 years, John Sealy Hospital No. 83393, was admitted Sept. 22, 1943, with a history of pain in the chest, nervousness, and weight loss, progressing during the preceding three months. There were no signs of congestive heart failure or of hyperthyroidism. The blood pressure was 110/80. The electrocardiogram showed paroxysmal atrial tachycardia, with an atrial rate of 188 per minute. The A-V conduction varied from 1:1 to 3:2 or 2:1 A-V block. Deep respiration and carotid sinus pressure increased the grade of block. The atrial mechanism was not interrupted by quinidine or digitalis administration. The patient was relieved of his symptoms by digitalization, which produced a fairly constant block with a slow ventricular rate. He died suddenly at home Nov. 24, 1943. Fig. 6, c, shows a strip of Leads I and III, taken in the sagittal and frontal planes on Oct. 26, 1943. Beside them is a three-dimensional model constructed from the data obtained from the curves for the three planes. This curve is exceptional in that, instead of passing down and to the right, as has been usual in the other cases of paroxysmal tachycardia, it curves up, backward, and to the left.

The characteristic feature of the curves derived during flutter and fibrillation is that the axes return to their initial direction, with cyclic repetition. In contrast, the curves obtained during paroxysmal tachy-

CASE 6.—O. J., a Negro man, aged 50 years, John Sealy Hospital No. 83208, was admitted Sept. 8, 1943, with congestive heart failure. He had had bronchial asthma since childhood. The exact anatomic cardiac diagnosis was uncertain. The abnormalities on examination included pulmonary emphysema; a basal diastolic murmur, loudest in the second left intercostal space; and roentgenologic evidence of en-

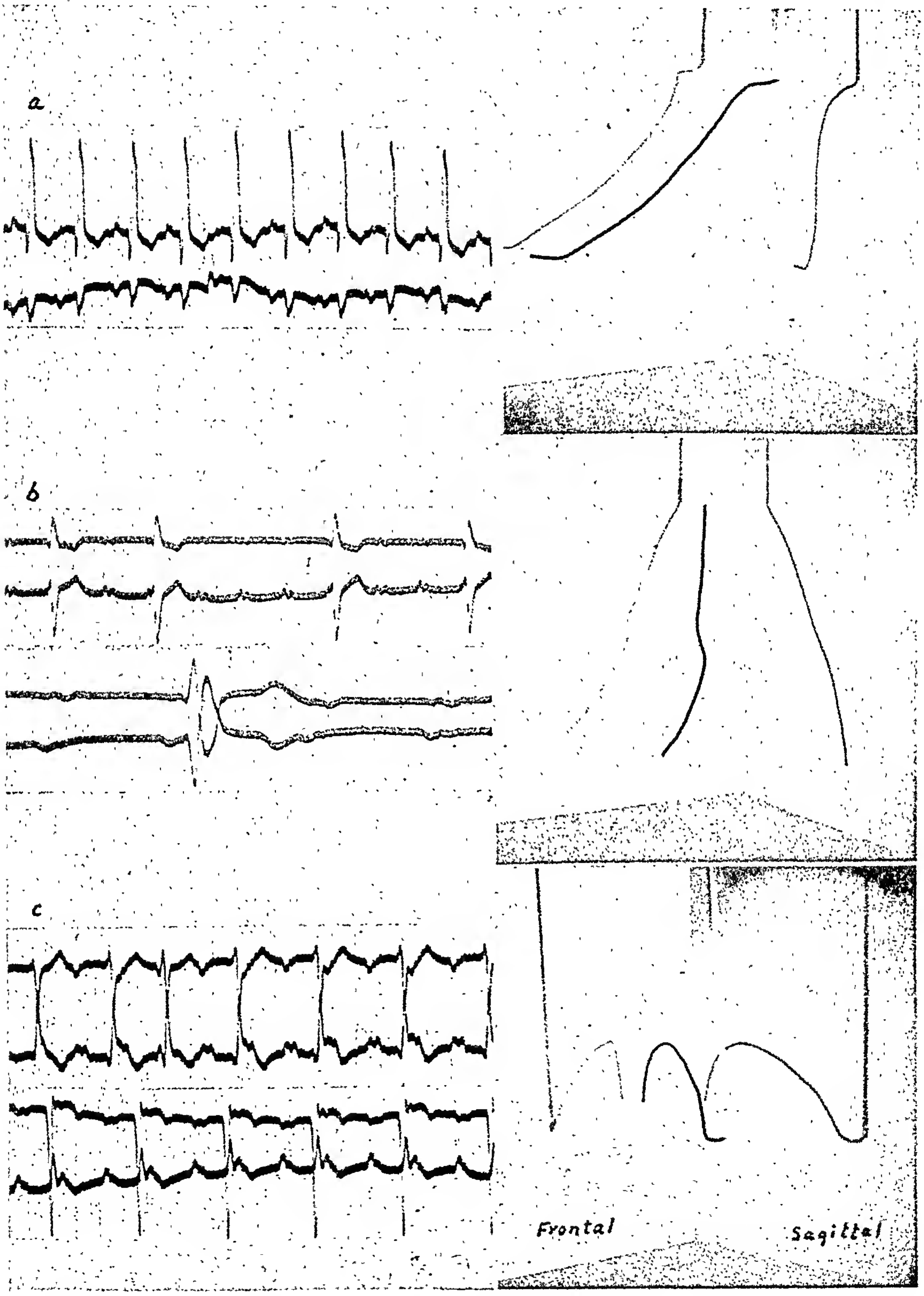

Fig. 6.—Axes during paroxysmal tachycardia. *a*, Leads I and III in the frontal plane, with the model of the atrial axes in Case 6. *b*, Case 7; limb Leads I and III above, with frontal plane Leads I and III at film speed of 75 mm. per second, below. Model on right. *c*, Case 8; Leads I and III of sagittal plane above, and frontal plane below, with photograph of model.

tachycardia, the vagus may cause A-V block or increase its degree, and may slow or stop the paroxysm. Barker, et al., have attributed the slowing and frequent interruption of atrial tachycardia which results from reflex vagal stimulation to depression of conduction of a circus movement as it passes through nodal tissue. This, of course, is entirely compatible with what is well known about vagal effects on A-V nodal tissue, although it does not take into account the occasional precipitation of a paroxysm by acetyl-β-methylcholine or by vagus stimulation.[11] Many cases of persistent paroxysmal tachycardia in which the A-V junctional tissue was depressed enough to produce some grade of A-V block have been reported. Of the eight cases studied above, in all except Case 6 there was A-V block. There is, unfortunately, a dearth of information about the action of the vagus, or of drugs, upon the rate of stimulus formation in the atrial muscle, but it seems reasonable to suppose that vagal stimulation may inhibit rhythmicity in an ectopic focus in a fashion similar to its effect commonly observed clinically on the rhythmicity of the S-A node, A-V node, and intervening tissues. This is borne out by the study of isolated atrial muscle strips made recently by Hiatt and Garrey,[14] which showed definite depression by acetylcholine of impulse initiation in the muscle.

The effects of the vagus on conduction in the atrial muscle probably do not need to be considered as bearing on this question. Vagal stimulation is without effect on atrial conduction at ordinary rates; it does, however, facilitate conduction by reducing the refractory period of the atrial muscle when this has been prolonged by such factors as cold, compression, fatigue, anoxemia, or rates above 300 per minute.[15] The higher atrial rates of flutter and fibrillation would lead us to expect a vagal facilitation of conduction through the pathways of the atrial muscle. When overdigitalization is a factor in producing the tachycardia, the refractory period will have been shortened by the drug.[16]

The contradictory implications of the occasional precipitation of paroxysms by digitalis, acetyl-β-methylcholine, and vagus stimulation, on the one hand, and by atropine, epinephrine, or vagus disease, degeneration, or inhibition, on the other hand,[17] cannot be explained in the light of our present knowledge of atrial muscle physiology.

Both quinidine and digitalis slow or stop paroxysmal tachycardia: both delay conduction in the A-V nodal tissue. Quinidine exerts this effect on conduction in the atrial muscle by raising the threshold to stimulation, according to Wedd, Blair, and Gosselin;[18] it also diminishes the rhythmicity of muscle strips.[19] Wedd, Blair, and Dwyer[20] have also shown that digitalis slows the rate of impulse formation, without change in threshold, in atrial muscle strips. Hence the effects of both of these drugs on paroxysmal tachycardia are compatible with their having acted upon an ectopic focus. The action of digitalis upon atrial muscle, or upon foci in the muscle, is not sufficiently clear to

cardia are, in general, like those obtained in sinus rhythm; most of them pass down and to the right, usually forward, occasionally backward; in one instance the curve moved up, backward, and to the left. In no instance was there any tendency for the curves to return to their original direction.

DISCUSSION

For the reasons that we have previously cited, we had anticipated that the curves derived during paroxysmal tachycardia would resemble those in flutter or fibrillation. Since we have failed to demonstrate this similarity, it seems necessary to consider carefully two possibilities, namely, (1) that the evidence which seems to support the likelihood of a circus movement may be viewed in such a light that it is compatible also with the existence instead of an ectopic pacemaker, and (2) that a circus movement may still pass through one of the nodes, but that only that portion involving the atrial muscle is perceptible electrocardiographically.

The limb leads do not give a strictly frontal plane projection, and the axes for the frontal plane cannot be approximated from the limb leads. This is probably because of the fact, which Schellong[11] has pointed out, that the arms and legs are not attached to the body at points in a plane, but are rather connected through large surfaces. Hence the electrical forces measured by the limb leads are derived not from the frontal plane alone, but from all the planes parallel to the frontal, and consequently are influenced by the projection on the sagittal, as well as the frontal, plane. For this reason the electrical axes apparent in the limb leads do not coincide with those of a planar projection, and conclusions based on that assumption are open to question. The axes estimated from the limb leads in the above cases were straight down, or slightly to the left and down, in five of the eight cases. In the other three the axes pointed up and to the left. In one of these, Case 8, the axis from the limb leads agreed roughly with part of the frontal plane projection of the three-dimensional momentary axis. This was the only instance of such agreement.

Of this small group of patients with paroxysmal tachycardia, seven fell into the type with A-V block which we have previously discussed.[1] They further bear out the conclusions previously drawn, namely, that myocardial disease and digitalis medication are important factors predisposing to this disturbance of cardiac mechanism. They show the marked irregularity of atrial rate also previously noted. We may note again the alternation of the P-P cycle length, with prolongation of the blocked cycle. We have attributed this to reflex vagal inhibition of the ectopic site of impulse formation, in a manner analogous to that which has been carefully analyzed by Ashman and Gouaux[12] in a patient with complete heart block.

Vagal stimulation increases the degree of A-V block in flutter and fibrillation, and may slightly increase the atrial rate; in paroxysmal

made during flutter, also, in each instance, exhibit a hiatus opposite to a long, relatively straight limb; the latter may perhaps correspond to that time during which Lewis found little change in the direction of the axis, and which he could not satisfactorily trace in the actual pathway of the experimental cases, namely, the time when the impulse was passing posteriorly along the area of the entrance of the great veins into the atria.

As a distinct contrast, we have presented[7] the curves illustrating the momentary shifts in the atrial electrical axes in persons with normal sinus rhythm, both normal and abnormal with respect to the position or size of the atria, or to the status of the atrial musculature. These curves often show large curvature, but fail to show any tendency to point finally in their original direction.

It is with these two large groups of cases, namely, sinus rhythm and a presumed circus movement, that we wish to compare the curves obtained from patients with paroxysmal atrial tachycardia. Most of the latter group show curves which clearly resemble those obtained during sinus rhythm, with the exception of their direction, which is usually down and to the right. They resemble in some instances the curves from patients with dextroposition of the heart; in other instances, curves from patients with mitral stenosis. Those which show large curvature still fail to manifest any tendency to repeat themselves, or to point finally in their original direction; nor is the degree of curvature greater than that which sometimes occurs with sinus rhythm, e.g., Case 1 or 2 during sinus rhythm.

We must admit the possibility that a circus movement residing chiefly in the nodal tissues might not be detected by our methods; we have pointed out, however, the virtual impossibility of such a circus in the A-V node in cases of tachycardia with A-V block, a view which Barker, et al., share. A circus elsewhere probably would be easily visualized by our method, although Lewis long ago pointed out that the atrial muscle did not afford enough room for a circus movement as slow as most paroxysms of tachycardia, at accepted rates of conduction.[25] The fact that these curves in paroxysmal tachycardia show no resemblance to those found in flutter or fibrillation, but are similar to those obtained during sinus rhythm, suggests to us that paroxysmal tachycardia is probably the result of the existence of an ectopic site of impulse formation, rather than of a circus movement. These curves may be modified, as are those of sinus rhythm, by the size and position of the atria and the status of the atrial muscle as a conducting medium, as well as by the site of origin of the exciting stimulus.

SUMMARY

Curves representing the consecutive atrial electrical axes for each 0.01 second have been derived for the frontal, horizontal, and sagittal planes

explain why digitalis should be the not infrequent cause of paroxysmal tachycardia, at least of the variety associated with A-V block. Its action upon the A-V conduction tissue is much better understood,[21] but none of its known effects at this point can explain why it causes paroxysms.

It might seem possible for paroxysmal tachycardia to be caused by a circus movement which passed through only a small part of the atrium, with the major portion of its pathway in the ramifications of the A-V junctional tissue, which may be very extensive, according to Kung and Mobitz[22] and Danielopolu and Proca.[23] These tissues are known to be most susceptible to those influences which depress conduction.[24] The persistence of such a circus in the presence of A-V block would require the assumption of selective block involving the fibers forming the A-V connection, but without block in the higher fibers. Nearly all tracings of paroxysmal tachycardia show some prolongation of the A-V conduction time. Occasionally, one with an unusually slow atrial rate will not; on the other hand, block as high as 6:1 has been recorded without interruption of the paroxysm.[1] Under these circumstances it does not seem justifiable to assume that a circus mechanism passes unhindered, at a rapid rate, through these highly susceptible tissues.

The S-A node is less easily subjected to study than is the A-V node, and there is far less information available about conduction through it. Lewis[25] has regarded this general area as part of the pathway of the circus movement which he has postulated as the cause of atrial flutter; his actual measurements in experimental flutter[25] included the "S-A nodal region," and showed no delay at this point in the passage of the impulse along its circular pathway. If the circus movement postulated for paroxysmal tachycardia includes an area comparable to Lewis' "S-A nodal region," it should be as readily demonstrable by our method as was the circus mechanism of atrial flutter in man by Lewis. This, of course, does not entirely exclude the possibility that the pathway includes nodal tissue whose electrical activity is presumably not measurable.

The data presented above are intended to put these questions to the test. Those presented in connection with atrial flutter and fibrillation are no different fundamentally from those of Lewis, although we have pictured them somewhat differently. They appear to support the idea that a circus movement may be present in these disturbances, although they offer no conclusive proof on this point. We have employed them merely for the purpose of showing what a presumed circus movement looks like when studied by this method. The characteristic feature of these figures is that, after a variable course, the axes return finally to their initial direction, and repeatedly inscribe a pathway which continues to conform to the general contour of a circus pathway. Those

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from patients with atrial flutter, atrial fibrillation, and paroxysmal tachycardia, and three-dimensional models have been constructed.

The clinical experimental results of Lewis, Drury, and Iliescu have been reproduced and extended in flutter and fibrillation.

The same procedure has been applied in eight cases of paroxysmal tachycardia. The type of curve in this disturbance of atrial mechanism has been found to resemble that obtained during sinus rhythm; it differs only in direction. The characteristic features of flutter and fibrillation are not present. This fails to support the idea that a circus movement is present in paroxysmal tachycardia, and although the possibility of a circus involving the S-A node is not finally excluded, we believe that the weight of the evidence points to the existence of an ectopic site of impulse generation.

The available information on the physiology and pharmacology of the atrial musculature and nodal tissues has been reconsidered insofar as it bears on the behavior of paroxysmal tachycardia, and the view that in it an ectopic pacemaker may be operative.

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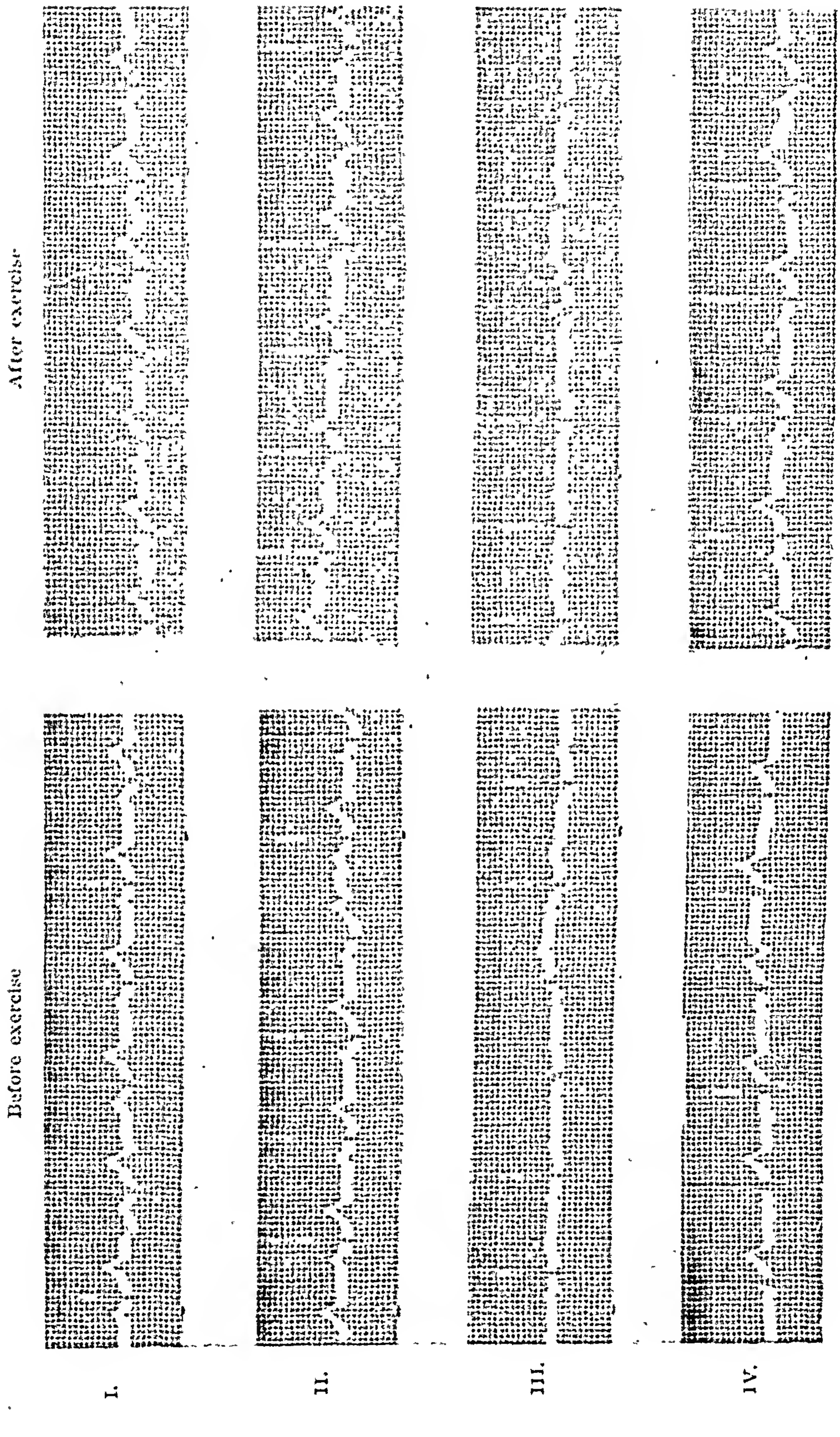

Fig. 1.—Electrocardiogram in Case 1 before and after climbing sixty steps.

THE ANGINAL SYNDROME AS A MANIFESTATION OF HYPERACTIVITY OF THE CAROTID SINUS

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SINCE the excellent clinical studies of Weiss and his associates,[1, 2] there have been many reports concerning hyperactivity of the carotid sinus. Many of these articles suggest that this interesting condition may be caused by, or at least be associated with, various pathologic states, such as arteriosclerotic heart disease,[3] hypertension,[4] biliary tract disease,[5] and cervical lymphadenopathy.[6] It has also been observed in cases of vegetative neurosis and digitalis intoxication.[7] In all of these conditions, the type of hyperactivity is vasovagal.

Although the diseases and drug intoxication listed above may make their presence first known by the manifestations of hyperactivity of the carotid sinus, it is also possible that the latter may in itself simulate a functional or organic disease. Thus, the carotid sinus syndrome with syncope may be confused with epilepsy, postural hypotension with collapse, the hyperventilation syndrome, or even with gastroenteritis.[8] I wish to report two cases in which the manifestations of hyperactivity of the carotid sinus simulated angina pectoris.

CASE REPORTS

CASE 1.—A medical officer, aged 35 years, was admitted to Tripler General Hospital Sept. 24, 1943. His complaint was of precordial pain beginning in the substernal area and radiating to the left hemithorax and shoulder.

The patient's past and family history was negative for cardiovascular disease.

The present illness began in February, 1943, at which time the patient began to experience sharp, pressing pain in the left hemithorax during periods of emotional tension. The pain, at the beginning, was only of several minutes' duration and seldom severe enough to be incapacitating.

On June 20, 1943, however, while carrying a heavy box a very short distance, the patient felt weak and dizzy, perspired very freely, and experienced a crushing sort of substernal pain which radiated to the left shoulder and upper part of the left arm. The pain disappeared within several minutes. Again on July 12, 1943, after a day of moderate activity, while walking on level ground and after experiencing the same symptoms as described immediately above, he fell to the ground, unconscious. A fellow medical officer, who was with him at the time of his syncope, stated that the patient's pulse could not be felt and that the skin became pale, cold, and clammy. He recovered consciousness within twenty seconds, but the pain in the chest and shoulder persisted for several more minutes. A similar attack, this time without syncope, occurred on August 9 as he was walking to his quarters, but he stopped, inhaled a pearl of amyl nitrite, and obtained immedi-

Received for publication Feb. 29, 1944.

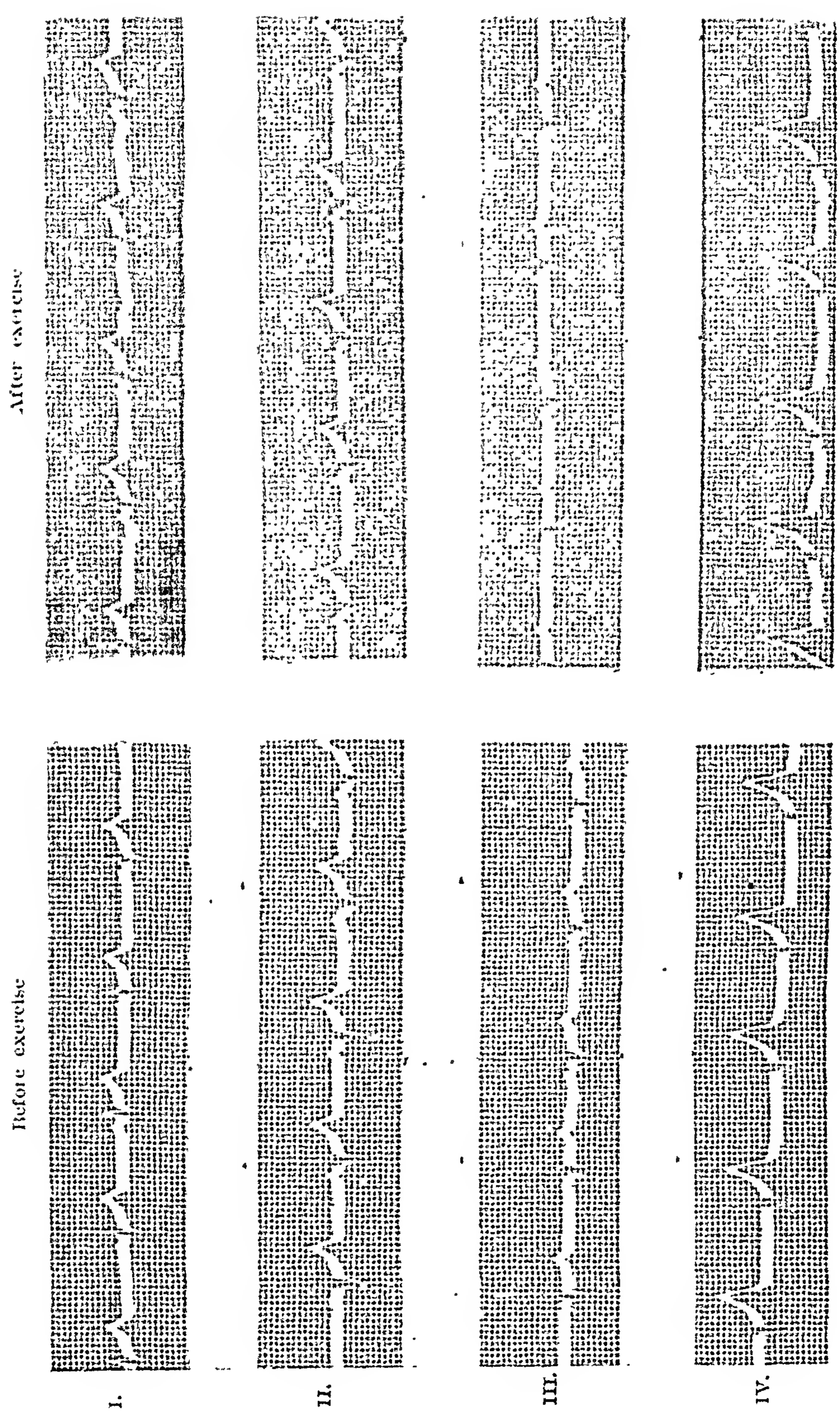

Fig. 2.—Electrocardiogram in Case 2 before and after climbing sixty steps.

ateate relief. On Aug. 21, 1943, the patient stooped over to place a golf ball upon a tee, and, while doing so, experienced extreme dizziness, weakness, and precordial pain with radiation to the shoulder and left arm. When he straightened up the symptoms immediately disappeared, and he was able to continue his game without further symptoms, despite the hilliness of the course. After this attack he had almost daily attacks of dizziness and anginal pain. He believed that he might be suffering from coronary artery disease with angina pectoris.

The patient was emphatic in declaring that exercise and exertion did not precipitate his anginal syndrome, but he admitted that sudden movements of his head frequently preceded the symptoms, although he had never before thought of the two phenomena as being related.

The patient was a well-developed person of healthy appearance. Other than dermatographia, excessive perspiration, easily produced urticaria (mechanical), and the reaction to massage of the right carotid sinus area, physical examination was negative. When massage was done, he became pale, perspired very freely, complained of dizziness and substernal pain, lost consciousness, and had several localized, clonic convulsions of the upper extremities. His blood pressure, which was 120/70 before massage, fell so low soon after the sinus was stimulated that it could not be measured. Concomitant with the fall in blood pressure, the heart rate slowed from 76 beats per minute to complete asystole soon after the onset of syncope. It was observed that the patient experienced his dizziness and precordial pain before the vasovagal effects occurred, and that syncope did not take place until the vasovagal effects became profound. The test was performed repeatedly and the same syndrome resulted almost invariably. An electrocardiogram taken during one such test showed complete asystole as the patient lost consciousness. The patient stated that the syndrome produced by carotid sinus massage was identical with that which he had had prior to his admission to the hospital.

While in the hospital, the patient went through various strenuous exercise tests (climbing stairs, running, jumping) which he did without abnormal symptoms or signs referable to his cardiovascular system. Electrocardiograms (Fig. 1) were taken before and immediately after the performance of very strenuous exercise. Both were normal and quite similar to each other. The basal metabolic rate was normal, and roentgenologic studies of the heart, urinalysis, examination of the blood, and serologic reactions showed nothing abnormal.

The patient was transferred to another hospital for further definitive treatment.

CASE 2.—A 21-year-old soldier was admitted to Tripler General Hospital Oct. 10, 1943. His complaint was of precordial pain beginning just lateral to the sternum and radiating to the left shoulder and left arm.

The patient's past and family history was negative for evidence of cardiovascular disease.

His illness began in 1937, at which time, while dancing, he suddenly became dizzy and was seized by a dull but intense pain in the left hemithorax which radiated to the left shoulder and arm. He immediately ceased dancing and the pain disappeared within several minutes. Thereafter he continued to have these attacks of dizziness and precordial pain, and, immediately prior to his hospital admission, he was having them every two or three days. He had observed that, although exercise did

disease. Both patients also denied that strenous exertion or heavy work induced attacks, although both were able to recollect that abrupt movements of the head might initiate the syndrome, an observation which in itself strongly suggests the presence of carotid sinus hypersensitivity. The frequent occurrence of syncope, with complete and instantaneous recovery, further indicated the true nature of their anginal syndrome. In coronary artery disease with angina pectoris, syncope rarely occurs unless profound changes have taken place in the heart itself—changes which will produce signs and symptoms which are not evanescent or of several minutes' duration as were those in our cases.

Besides the differentiation allowed by the facts culled from the histories of these two patients, the physical examination further clarified the diagnosis. The discovery that the carotid sinus was hypersensitive, and the reproduction of the syndrome from which they suffered prior to admission by stimulation of the sensitive sinus pointed to the true cause of the difficulty. The negative evidence for cardiovascular disease afforded by the electrocardiogram, the roentgenogram, the exercise tests, and other laboratory data further secured the diagnosis of carotid sinus syndrome.

The converse of the present syndrome has been reported by Sigler[3] to occur in cases of proved organic heart disease, namely, that hyperactivity of the carotid sinus mechanism frequently may be found in arteriosclerotic heart disease. He further describes this carotid sinus syndrome as cardio-inhibitory in nature. If this is true, the possibility of hyperactivity of the carotid sinus must be kept in mind not only as a process initiated by a diseased heart, but also as a process which in itself may simulate the symptoms arising from disease of the heart. The evaluation of any history of vertigo, anginal pain, and syncope must be doubly cautious if error is to be avoided. But if the history is not typical of coronary artery disease; if there have been attacks of vertigo and syncope; if this history is coupled with the presence of hyperactivity of the carotid sinus, which, on stimulation, reproduces the patient's symptoms (particularly with no vasovagal changes); and if there are no organic, functional, or laboratory indications of cardiovascular disease, even on severe exertion, it would be most unfair to the patient to tell him that he had organic heart disease. It would be more expedient to hold such a diagnosis in abeyance until objective signs of organic heart disease make their appearance—a phenomenon which probably will not occur in such cases.

SUMMARY

1. Two cases of carotid sinus syndrome are reported in which anginal pain, similar to that associated with cardiac ischemia, occurred as a manifestation of hyperactivity of the carotid sinus.

not induce an attack, sudden movements of his head might easily provoke one. Consequently, he made it a point to turn his head slowly and not to bend over rapidly to tie his shoe laces; otherwise, he would become dizzy and have the anginal pain. He fainted several times on such occasions, but always recovered consciousness within ten to fifteen seconds and had no apparent sequelae. On admission, the patient was convinced that he had serious heart disease.

The patient was poorly developed; his state of nutrition was fair, but he exhibited signs of profound anxiety. The remainder of the physical examination was completely negative except that the right carotid sinus was hypersensitive. When the latter was massaged with the patient in the sitting position, he began to complain of dizziness and anginal pain identical with that which he experienced before admission to the hospital. When the massage was continued, the patient lapsed into syncope. Unlike Case 1, however, no significant vasovagal effects followed massage, either before, during, or after syncope. Thus, the heart rate and blood pressure were 80 per minute and 110/80, respectively, before sinus massage, and, as he became unconscious, the heart rate and blood pressure were 74 per minute and 120/75, respectively, with little change during syncope or immediately afterwards. The test was repeated many times and the same syndrome invariably occurred. One milligram of atropine, administered parenterally, did not prevent induction of the syndrome.

This patient, also, was made to take various exercise tests (climbing steps, running, jumping), but he never experienced dizziness, anginal pain, or any other abnormal cardiovascular symptom during or immediately after the performance of such tests. The electrocardiogram (Fig. 2) was normal both before and after exercise. The sedimentation rate and basal metabolic rate were normal. Roentgenologic studies of the heart, urinalysis, examination of the blood, and serologic reactions were negative.

The patient was transferred to another hospital for further treatment.

DISCUSSION

The occurrence of precordial pain, dyspnea, and collapse strongly suggests the possibility of coronary artery disease. It is noteworthy that one of our patients, himself a physician, believed that he might be suffering from coronary artery disease with angina pectoris, and had taken amyl nitrite for relief. Thus, any syndrome arising from an extracardiac source which produces symptoms similar to those frequently associated with cardiac ischemia or infarct may prove difficult to differentiate from a syndrome caused by organic heart disease. This becomes understandable when one remembers that, in many cases, the diagnosis of coronary artery disease[3] may be made only by the history obtained from the patient.

In the histories of the two patients reported herein, however, certain facts were elicited which clearly indicated the essential nature of the disorder, allowing differentiation from the syndrome of angina pectoris associated with coronary artery disease. Thus, both patients emphasized the frequent occurrence of vertigo preceding the anginal pain, which is not commonly seen in patients suffering with coronary artery

PHYSIOLOGIC EFFECTS OF CARBON DIOXIDE WATER BATHS ON ALVEOLAR CARBON DIOXIDE TENSION, SKIN TEMPERATURE, AND RESPIRATORY METABOLISM

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INTRODUCTION

IN STUDYING the influence of carbon dioxide mineral water baths on the circulation, observations on the changes in alveolar carbon dioxide tension, skin temperature, and respiratory metabolism have been made. The results indicate that definite increases occur in the alveolar carbon dioxide tension and in the amount of carbon dioxide eliminated through the lungs when the subject is submerged in the natural carbon dioxide mineral waters. These changes do not appear when the same subject is exposed to plain water.

PROCEDURES

A. Alveolar Carbon Dioxide Tension.—A special experimental room was equipped to carry out these observations. It contained a large tub (200 gallons), into which hot or cold water, carbon dioxide mineral water, or plain water could be drawn. Over this tub a sponge-rubber-covered stretcher was suspended. The stretcher was fitted with a foot-rest, an adjustable reclining back, and a headrest, enabling the patient to rest comfortably in a semireclining position during the entire observation. A pulley arrangement made it possible for the operator to lower the stretcher and patient into the tub and take him out again without any effort or motion on the part of the patient (Fig. 1). During the entire experimental period, the patient's mouth and nose were covered with a rubber mask with an inflated edge. This was connected to a set of flutter valves by means of kink-proof tubes (as shown in Fig. 1), and allowed the patient to breathe outdoor air. The mask was removed only for the few seconds necessary to obtain the alveolar sample by means of the Henderson-Morriss tube.[1]

The experiments were conducted from 9 to 10 A.M., about one and one-half hours after the patient had had a standard breakfast. He was allowed to rest for twenty minutes with the face mask attached. During this period, the bath, either of carbon dioxide or plain water, was drawn at 35° C. (95° F.). The carbon dioxide baths were prepared with the natural mineral water from the Lincoln Springs in the manner used in regular mineral water baths at The Saratoga Spa. They contained a supersaturation of 30 to 34 per cent carbon dioxide by volume.

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These studies were supported in part through funds administered by the New York State Department of Health.
Received for publication March 9, 1944.

2. Stimulation of the hyperactive carotid sinus reproduced the anginal syndrome in both cases.

3. The differentiation of anginal pain associated with the carotid sinus syndrome from that associated with cardiac ischemia secondary to coronary artery disease is discussed.

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TABLE I

TYPICAL PROTOCOL

EXPERIMENT 9		
TIME (A.M.)	PROCEDURE	TOTAL NUMBER OF MINUTES
7:30	Standard Breakfast Tomato juice 2 slices of buttered toast 1 cup of coffee with cream and sugar	
8:30 to 9:07	Rest period on cot in experimental room	37
9:08	Patient transfers from cot to stretcher suspended over tub	
9:10	Mask attached over nose and mouth of patient	5
9:12	Carbon dioxide mineral bath drawn	8
9:15	Washing out of dead space in Tissot machine	3
9:18	Tissot emptied and spirometer set at zero	1
9:19 9:24	Base run started Base run ended	5
9:24 to 9:26	Gas volume and temperature reading of base run	2
9:26	Stretcher with patient lowered into a 35° C. mineral water bath containing 34 per cent supersaturation of carbon dioxide by volume	
9:26 to 9:29	Two one-minute washouts of machine	3
9:30 9:35	Second test started (Procedure same as base run) Second test ended	5
9:35 to 9:37	Gas volume and temperature reading	2
9:37	Two one-minute washouts of machine (Procedures same as base run)	3
9:40 9:45	Third test started (Procedure same as base run) Third test completed	5
9:45	Stretcher and patient raised out of the tub. Patient dried with towels without rubbing, and covered with a warm sheet and light blanket. Ten-minute rest with mask still attached	10
9:55	Two one-minute washouts of machine	3
9:59 10:04	Fourth and last test started Last test completed	5

B. Skin Temperatures.—For the study of changes in skin temperature, observations were made at four different temperature levels, namely, 29.4° C. (85° F.), 32.2° C. (90° F.), 35° C. (95° F.), and 37.8° C. (100° F.). No changes occurred in the bath temperatures during the periods of observation. The baths were given from 9 to 10 A.M., after the patient had had a standard breakfast. Two series of baths were made at each temperature level, on each subject, usually on successive days. On the starting day of a series the plain water bath was given first, followed by the carbon dioxide water bath, and, on the next day, the order of the baths was reversed. Eighty bath series were given to six men who were physically normal. The patient was im-

After the rest period, when pulse and respiration had reached a constant level, the base alveolar sample was taken. The patient was lowered into a 35° C. mineral water or plain water bath, and alveolar samples were taken at the fourth, eighth, twelfth, and sixteenth minutes. Then the patient was raised from the bath, dried, covered, and allowed to rest (still attached to the mask). Alveolar samples were taken ten and twenty minutes after the bath. The same procedure was used in the bath series with the patient breathing room air except that the inhale valve of the mask was not attached to the outdoor air inlet. This allowed the patient to breathe the air above the tub.

The samples of room air, outdoor air, and alveolar air were collected in mercury-evacuated Bailey sampling bottles.[2] All samples were analyzed for carbon dioxide in duplicate in a Haldane-Boothby-Sandiford gas analysis apparatus, with an accuracy of ± .01 per cent, and duplicate analyses had to check within these limits. Complete analyses of outdoor

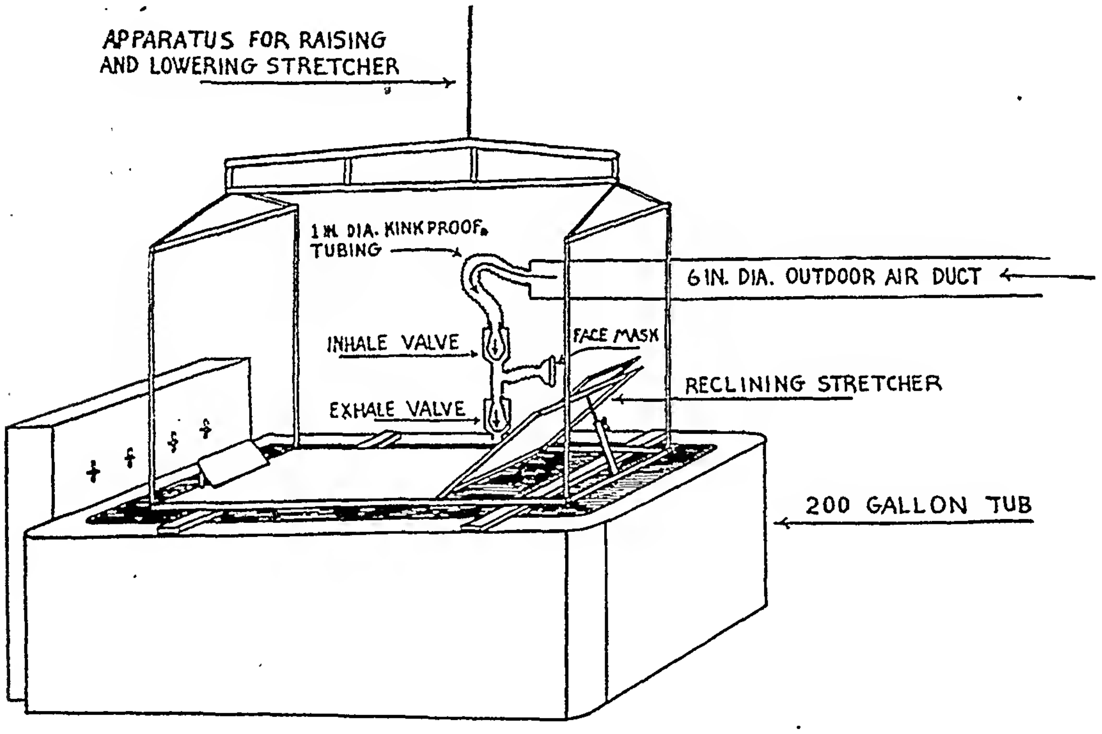

Fig. 1.—Plan of experimental setup. The experimental tub has pipe connections for both hot and cold, plain and mineral, water. The stretcher is suspended over the tub with a mechanical device for lowering and raising the stretcher and patient into and out of the bath without any effort on the part of the patient. It shows the air connections from outside to the mask, so that the patient may breathe outside air during the entire observation.

air were made from time to time to check on the accuracy of the machine and to make sure that the patient was breathing air with .03 to .04 per cent carbon dioxide. The room temperature was recorded, and ranged from 25° C. to 30° C., but did not vary more than 0.5° C. during any experimental period. Barometric readings were taken, and the carbon dioxide tensions were calculated by means of the formula:[1]

$$P_{CO_2} = \frac{C}{100} \times (B - W)$$

P_{CO_2} = Carbon dioxide pressure in millimeters of mercury at 38° C.
C = Percentage of carbon dioxide in alveolar sample
B = Recorded barometric pressure in millimeters of mercury
W = Pressure in millimeters of mercury of water at 38° C.

studied in a bath of plain water to which 5 pounds of sodium chloride and 5 pounds of sodium bicarbonate were added in order to simulate the mineral content of the natural mineral water without the carbon dioxide.

The personal data regarding the fifteen subjects used in these studies are presented in Table II. Reference to individual observations will be made by the numbers indicated in this table.

EXPERIMENTAL DATA

A. *Alveolar Carbon Dioxide Tension.*—A series of tests were carried out to ascertain the concentration of carbon dioxide gas in the air above the tub. The averages of these data are presented in Tables III and IV.

We found by measurement that the patient's nose and mouth were about 3 inches above the top of the tub, and four experiments were made to ascertain the effect of time on the carbon dioxide gas concentration above the bath at this level.

These data made it evident that the patient must breathe outdoor air in order to study carbon dioxide absorption from the bath. This was accomplished by attaching the patient to the mask and valves as already described (Fig. 1). Analyses of the air that the patient was breathing while attached to this setup never showed more than 0.04 per cent carbon dioxide, and agreed with Carpenter's[4] observations as to the constancy of the outdoor air.

Sixty-two experimental baths at 35° C. were given to seven different male subjects. Two men had less than 85 per cent of normal vital capacity, but showed the same type of results as those subjects with normal vital capacity. These two showed greater variability in results than the other subjects.

Since only one experimental run was made each day, differences in the physiologic state of the subject were indicated by variations of alveolar carbon dioxide tension at the end of the initial rest period.

TABLE III

35° C.—CARBON DIOXIDE WATER BATH*—WITH AND WITHOUT PATIENT

	TOP OF TUB	3 INCHES ABOVE TOP	6 INCHES ABOVE TOP	12 INCHES ABOVE TOP
No patient	4.28†	.54	.55	.55
Patient in tub	----	2.26	1.84	1.82

*Samples were taken as soon as bath was drawn.
†Percentage of carbon dioxide.

TABLE IV

35° C.—CARBON DIOXIDE WATER BATH*—PATIENT IN TUB

	START	3 MIN.	6 MIN.	9 MIN.	12 MIN.	16 MIN.
Patient in tub	2.44†	1.34	1.01	.65	.68	.56

*Average of samples taken at height of patient's nose.
†Percentage of carbon dioxide.

TABLE II

PERSONAL DATA—EXPERIMENTAL SUBJECTS

NUMBER	NAME	SEX	AGE (YR.)	WEIGHT (LB.)
1	W. C.	M	64	172
2	C. E.	M	50	180
3	W. M.	M	46	175
4	A. D.	M	43	215
5	C. G.	M	19	155
6	R. V.	M	45	136
7	D. B.	F	25	125
8	J. C.	M	29	137
9	T. A.	M	40	156
10	G. D.	M	37	133
11	H. F.	F	36	200
12	E. D.	M	29	130
13	Q. C.	M	22	128
14	L. P.	M	25	140
15	J. S.	M	18	128

mersed to shoulder level in a carbon dioxide or plain water bath at the given temperature. Each minute he put either his right or left foot on a small platform fastened to the side of the tub, and the toe and instep were immediately blotted dry with absorbent paper. Skin temperature readings (using the Taylor dermatherm) were taken of each foot on alternating minutes during the sixteen-minute bath. The thermocouple was applied to the great toe and instep of each foot, and both readings were completed within fifteen seconds. Between the baths, the patient reclined on a couch in the experimental room. The room temperature was recorded, and ranged from 27° C. to 35° C., but did not vary more than 1° C. during any experimental period. These observations were made during June, July, and August, which accounts for the occasionally high room temperatures in the series.

C. Respiratory Metabolism.—For the study of the respiratory metabolism a Tissot spirometer was used to collect the expired air of patients for four separate periods. The first, or base period sample, was taken with the patient resting on the stretcher over the tub, the second and third period collections were made with the patient in the bath, and the fourth period sample was taken ten to fifteen minutes after the patient was removed from the bath but while he was still resting on the stretcher. Expired air was collected in a Tissot spirometer for the study of respiratory metabolism, as described by Bailey.[2] Samples of the expired air were analyzed in a Haldane-Boothby-Sandiford machine according to the procedures outlined by Boothby and Sandiford.[3] Table I gives a protocol of the experimental procedure. This procedure was uniform for all the bathing experiments.

Four types of observations were made. In order to accustom the subject to the procedure, all of the steps in Table I were followed in a preliminary observation, except that no bath was drawn in the experimental tub. The data obtained covered a training period for the subject, and were used for additional check on other controls. In all instances at least two experimental observations were made, one in which the natural-carbonated mineral water was used in the bath, and a second when plain water at the same temperature was used. In three cases repeated series of observations were made, so that a total of ten comparable sets of data were obtained. In addition, two subjects were

TABLE VI

MEAN ALVEOLAR CARBON DIOXIDE TENSION IN 35° C. BATHS

	CO_2 WATER—PATIENT BREATHES OUTDOOR AIR	PLAIN WATER—PATIENT BREATHES OUTDOOR AIR	CO_2 WATER—PATIENT BREATHES ROOM AIR	PLAIN WATER—PATIENT BREATHES ROOM AIR
Base alveolar tension after 20-minute rest	40.6*	40.7	42.6	41.9
4 minutes in bath	42.9	40.7	45.2	42.3
8 minutes in bath	43.3	40.5	45.7	41.8
12 minutes in bath	43.4	40.5	46.0	41.4
16 minutes in bath	43.1	40.6	45.7	41.4
10 minutes after bath	41.2	40.2	45.0	41.7
20 minutes after bath	40.7	40.2	43.1	41.8
Maximum rise above base	2.8	0.0	3.4	0.4
Percentage rise above base	6.9	0.0	8.0	0.9

*P_{CO_2} = millimeters of mercury at 38° C., dry.

ences were noted between the two curves. The starting skin temperatures of the instep were 0.5° C. to 1° C. higher than those of the toe, but during the baths they approached the same level. For the sake of brevity, only the skin temperatures of the great toe are included.

Series 1, consisting of plain and carbon dioxide mineral water baths at 29.4° C., showed no marked differences in skin temperatures between the carbon dioxide water, and plain water, baths. The skin temperature dropped to a level 0.5 to 1° C. above the bath temperature. Series 2, at 32.2° C., showed nearly the same results as Series 1, but there was a tendency for the skin temperature to be higher in the carbon dioxide water baths. In both these series, the patients felt slightly chilly while in the tub. In Series 1 the skin temperatures were above the bath temperature, and, in Series 2, 3, and 4, the skin temperatures were below the bath temperature.

Series 3, at 35° C., and Series 4, at 37.8° C., showed consistently higher skin temperatures in the carbon dioxide baths. The readings were 0.5 to 1° C. higher at the end of the carbon dioxide water bath. This difference was noted in the skin temperatures of all the patients, and therefore it is considered of some significance. In the baths at 35° C. (Series 3), the skin temperature rose to a point 1.5 to 2° C. below the bath temperature, and then leveled off. In the baths at 37.8° C. (Series 4), the nearest approach was 2.5 to 3° C. below the bath temperature. Typical results of each bath series are shown in Fig. 3.

The order in which the baths were given had no measurable effect on the results. Series in which the plain water bath was given before the carbon dioxide water bath showed almost the same curves as when the reverse order was used. All the subjects had a distinct hyperemia of the skin when they emerged from the carbon dioxide water baths. The hyperemia was confined to the area of the body covered by the carbon dioxide water, with a distinct line of demarkation between the

However, the general direction of each set of observations was determined by the experimental procedure used, and was not dependent on the level of the resting alveolar tension. To check this, two experiments were made in which the patient took no bath, but went through all the movements and samplings used in the regular procedure. The average results of these two tests, as presented in Table V, indicate the small amount of variation inherent in the technique.

TABLE V

	AFTER 20-MINUTE REST PERIOD	4 MINUTES IN TUB, NO WATER	8 MINUTES IN TUB, NO WATER	12 MINUTES IN TUB, NO WATER	16 MINUTES IN TUB, NO WATER	10 MINUTES OUT OF TUB	20 MINUTES OUT OF TUB
P_{CO_2} mm. Hg at 38° C., dry	43.0	42.4	42.2	42.2	42.0	42.8	43.0

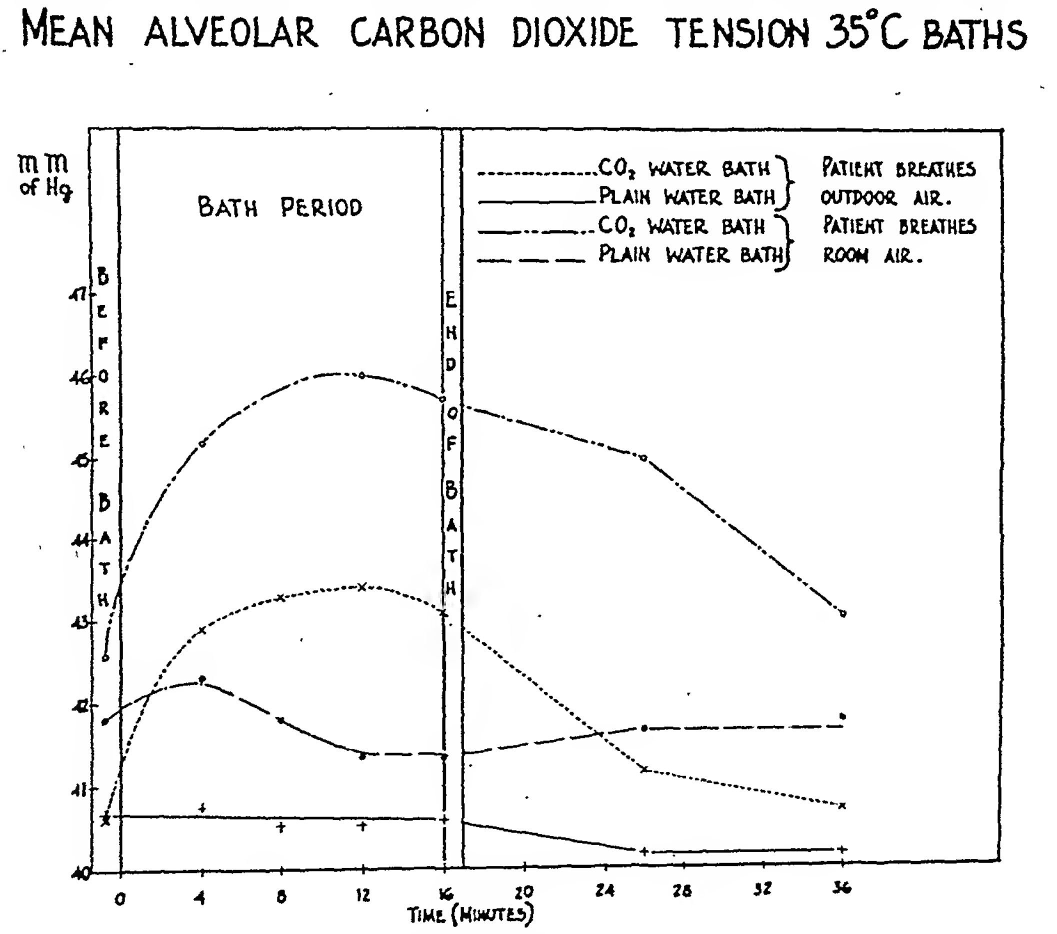

Fig. 2.—The curves show the levels of alveolar carbon dioxide tension during the base period before the bath, with subsequent changes in and after both the mineral and the plain water baths. Observations were made as indicated when the patient breathed outside air (———— and --------) and when he breathed the air over the tub (—.— and—. .—).

The carbon dioxide concentration in the alveolar air is presented as tension in millimeters of mercury at 38° C., dry. The mean results of the four different experimental procedures are shown in Table VI, and are presented graphically in Fig. 2.

B. *Skin Temperature.*—Skin temperature observations on the great toe and instep were made at each reading, but no significant differ-

TABLE VII

RESPIRATORY DATA*

PERIOD	CARBON DIOXIDE ELIMINATED (C.C./MIN.)	OXYGEN ABSORBED (C.C./MIN.)	RESPIRATORY QUOTIENT	MINUTE VOLUME LITERS
Mineral				
Base run	190.6	194.0	0.98	6.03
In bath	226.4	194.5	1.16	6.71
In bath	236.3	187.9	1.26	7.01
After bath	192.9	195.9	0.99	6.06
Plain				
Base run	190.7	197.1	0.97	6.04
In bath	186.6	190.8	0.98	5.73
In bath	186.5	193.3	0.97	5.77
After bath	187.8	195.9	0.96	5.88

*Each figure in the table represents the mean average of the ten comparable observations on the seven subjects studied.

increase which varied from a minimum of 22 to a maximum of 68 c.c. per minute. In the period following the bath the variations showed an equal number of increases and decreases.

The carbon dioxide elimination which occurred during the plain water bath was entirely different; in the large majority of observations there was a slight decrease which was not considered of real significance. Also, in the period after the bath the elimination of carbon dioxide was at the same level as during and before the bath in plain water.

Oxygen consumption: The oxygen consumption during these observations showed no consistent variation from the base period in either the mineral or plain water baths. The number of observations showing decreases practically equalled the number in which increases occurred. In either case, the variation from the base period was not considered significant.

Respiratory quotient: From the data obtained for the carbon dioxide elimination and the oxygen consumption during these studies it follows that a marked increase in the respiratory quotient would occur. During the periods in the carbon dioxide baths this change was noted, as indicated in Fig. 4. Respiratory quotients as high as 1.3 were obtained in some cases.

The quotients for the base periods cannot be considered basal because all observations were made following a light, standard breakfast. This breakfast was largely carbohydrate, and, therefore, many quotients were above the usual basal level. The type of mask which could be obtained for these observations had only a single outlet. This increased slightly the usual dead space, not sufficiently to produce discomfort, but apparently enough to cause slight variations in obtaining exact figures for the actual amount of oxygen consumed. This experimental factor was recognized, but it is not felt that it materially influenced the variations which occurred when comparable observations were made on the different subjects.

immersed and unimmersed skin areas. This was not present when the patient emerged from the plain water bath.

C. *Respiratory Quotient.*—The material assembled from these studies on seven subjects is presented as mean averages in Table VII. Data covering the amount of carbon dioxide eliminated and of oxygen consumed, the respiratory quotient, and the respiratory minute volume during the mineral and the plain water baths are presented.

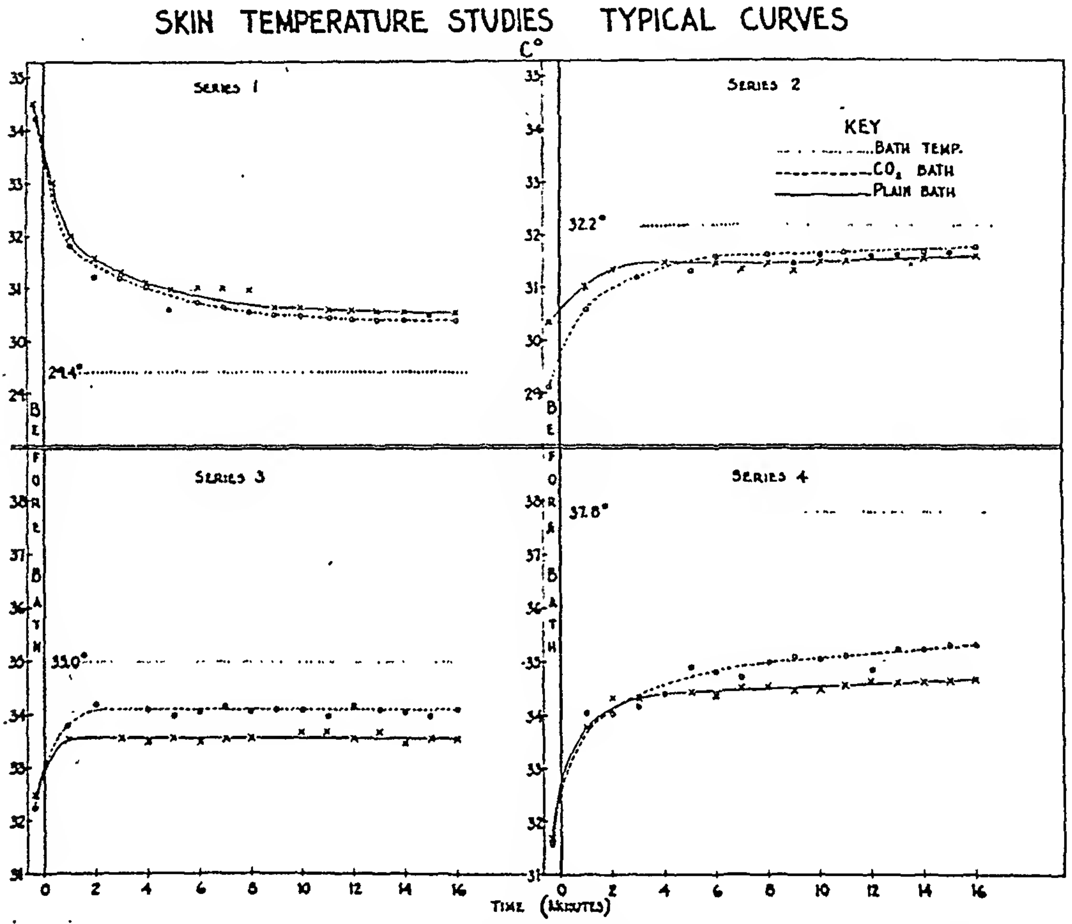

Fig. 3.—The curves are drawn from data plotted to represent the average of the observed temperatures. The starting temperature is influenced by the room temperature, which is recorded in the table. In all observations the temperature shifted toward the temperature of the bath, and, within two to four minutes, reached a relatively constant level except in the carbon dioxide bath at 37.8° C., where the curve continued to rise slowly during the entire observation.

In order to show the individual results in the seven subjects studied, the actual variations obtained in periods two, three, and four, as compared to the base period in each of the experimental observations, have been calculated and are presented in Fig. 4. The variations in these data which were greater than the base period are represented by columns extending upwards from the base, or zero, line. The variations which represent a decrease in the findings are indicated by columns extending downward from the base line.

Carbon dioxide: It will be seen from a study of Fig. 4 that striking changes occurred in the carbon dioxide elimination during the two periods in the mineral water bath. In all observations there was an

TABLE VIII

ANALYSES NATURAL MINERAL WATER AND ARTIFICIAL SALINE WATER

	DATE	CHLORINITY (MG./LITER)	ALKALINITY (MG./LITER)
Lincoln water (natural mineral)	12/2/42	1835	2295
Artificial saline water	12/2/42	2260	2115
Artificial saline water	1/5/43	2180	2055

DISCUSSION

There has been much speculation and experimentation relating to the interchange of carbon dioxide through the skin. Hediger,[5] in a series of carefully controlled experiments, showed that carbon dioxide dissolved in water could pass through the skin. Chambers with a side opening containing water with different concentrations of carbon dioxide were sealed against the skin. The carbon dioxide diffused out of those chambers which contained more than 4 volumes per cent. and those with less than this amount took up carbon dioxide until the concentration reached 3.8 volumes per cent. Cobet and Häbler,[6] Groedel and Wachter,[7] and Harpuder,[8] using other experimental methods, confirmed Hediger's observations. Their work showed that changes occur in the respiration and blood picture when patients are given carbon dioxide baths which could best be explained by the passage of carbon dioxide through the skin. Recent studies by Stein and Weinstein[9] showed that significant and prolonged elevation of the skin temperatures of patients resulted from using artificial carbon dioxide baths on the lower extremities. They also demonstrated capillary dilatation by means of a capillary microscope with a photographic recording apparatus. In this study, they found that both the arterial and venous limbs of the capillaries were larger, and that the blood flow was greater when the limb was exposed to the water containing carbon dioxide. They considered that these observations supported the idea that dilatation of the smaller vessels occurred, and that the increase of blood flow recorded by their plethysmographic studies suggested that this dilatation may have occurred also in the larger vessels of the extremities.

A. *Alveolar Carbon Dioxide Tension.*—Certain changes in the blood picture can be studied by means of alveolar air sampling, as pointed out by Carpenter and Lee[10] and Cournand, Baldwin, et al.[11] Cournand and Richards[12] state that the carbon dioxide tension in the blood of normal persons tends to remain at a constant level. Carpenter and Lee[10] found that, with a trained subject, the alveolar carbon dioxide, taken at fifteen-minute periods on two different days, showed the results given in Table IX.

It was necessary to know the variation inherent in the technique to ascertain whether or not the observed changes were significant. The actual variation in the alveolar CO_2 tension in the control experiments

Minute volume: A definite increase in the minute volume output of the subjects during the carbon dioxide bath was noted. It occurred in all but one observation. The variations reported in the figure showed a wider range of increase than was found in the carbon dioxide eliminated. The variations in the minute volume during the plain water baths, for the most part, showed some decrease from the base period.

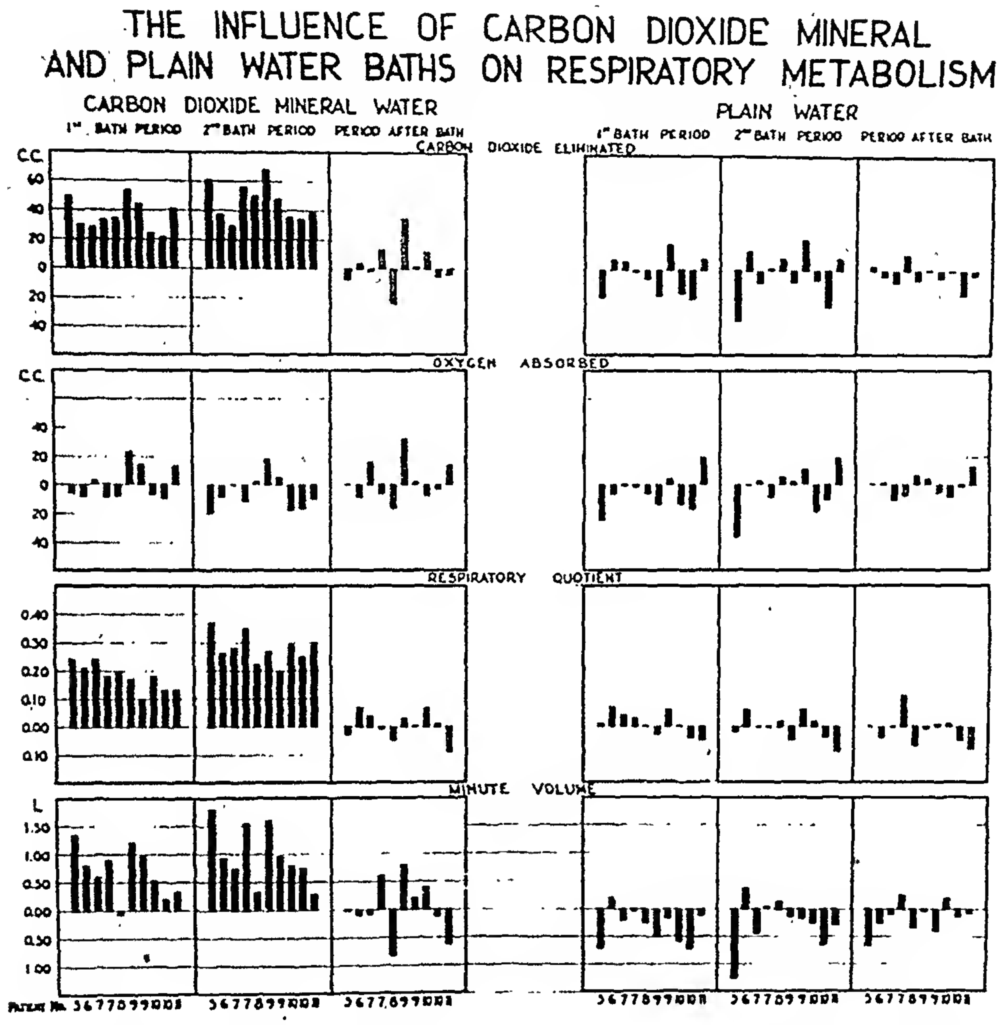

Fig. 4.—Each column represents the actual variation from the base period data of carbon dioxide, oxygen, respiratory quotient, and minute volume obtained during the periods in and after the bath. Columns extending upward from the zero line indicate increases, and those downward show decreases.

Artificial saline baths: In order to check the influence of the saline constituents in the mineral water baths without the carbon dioxide, two subjects were tested in plain water baths to which were added sodium chloride and sodium bicarbonate in amounts similar to those present in the mineral water. In this bath the subjects were exposed to all of the effects of the mineral water except the carbon dioxide. The metabolic data obtained from these two experiments showed no appreciable variation from those obtained from the same subjects in the plain water bath. Table VIII presents actual data of the analysis of the water used in this prepared bath, with a comparison to similar data obtained on the natural mineral water from the Lincoln Springs.

carbon dioxide bath. A reversal of the order of giving the baths was made in every series; therefore, the subject acted as his own control, and the changes observed appear to be the result of the carbon dioxide baths. Definite, visible hyperemia of the skin was noted over the immersed area of the patients when they emerged from the carbon dioxide baths. It was not present when the subject emerged from the plain water bath.

Eighty baths were given to six normal subjects. Although their ages ranged from 18 to 46 years, much the same results were obtained in duplicate sets of experiments on each patient. Certain patients showed greater skin temperature changes than others, but all followed the same general curves. As noted in Fig. 3, the skin temperature showed considerable variations before entering the bath. These variations may have been due to differences in room temperature (27 to 34° C.), or to the general physiologic state of the patient on different days. However, these differences were eliminated within two minutes after the subject entered the bath, and the differences observed after that period are considered as a result of the influence of the baths.

The subjects were observed at four different temperature levels, and the variations noted were more evident when the bath temperature was near body temperature. The observations in a cool bath at 29.4° C. and 32.2° C. showed that the temperature of the water, rather than the action of carbon dioxide, apparently exerted the principal influence. The curves approached similar levels and did not show significant differences between the two types of baths at these temperatures.

The tendency of the skin temperature to adjust to the temperature of the surrounding medium was also evident in the warmer baths at 35° C. and 37.8° C. Here, however, the skin temperature rose to a higher level with the subject in a bath of carbon dioxide water than it did when plain water was used. The differences noted were not striking, but, when taken with the other data obtained, they point to the correctness of the idea presented by Harpuder[8] and others, namely, that carbon dioxide is absorbed through the skin and produces an effect by direct influence on the capillary network.

C. *Respiratory Metabolism*.—In considering the data presented in this section it is important to analyze certain features to ascertain whether or not the observations indicate that carbon dioxide is absorbed from the bath through the skin. The experimental data show without question that, during the exposure of the body to a mineral water bath containing large quantities of carbon dioxide in both free and combined form, there is a definite increase in the amount of carbon dioxide eliminated through the lungs without a corresponding increase in oxygen consumption. This combination results, of course, in a marked elevation in the calculated respiratory quotient. There was also an increase in the respiratory minute volume, but this was considerably less constant than the increase in elimination of carbon dioxide.

TABLE IX

DATE	NUMBER OF DETERMINATIONS	AVERAGE ALVEOLAR CO_2 PER CENT	AVERAGE ALVEOLAR CO_2 TENSION (P_{CO_2})
May 7	20	5.97 ± 0.11	42.4*± 0.7
May 16	25	5.98 ± 0.12	41.9 ± 0.8

*Approximate (calculated from Carpenter's data, assuming temperature at 38° C. and pressure at 760 mm.)

(Table V) was only 1 mm. of mercury. The changes that occurred in plain water baths varied only slightly from that figure, but the alveolar carbon dioxide tension in the carbon dioxide water baths ranges from 2.1 to 6.3 mm. of mercury, a rise of 5 to 10 per cent above the resting level. The changes observed in carbon dioxide baths are produced by some factor which is not present in the plain water baths.

The small changes in alveolar carbon dioxide tension during the plain water baths are probably caused by the general relaxing effect of 35° baths and changes in breathing due to the pressure of the water. When the patient is lowered into the tub there is a slight shock because of the difference between the skin temperature and the water temperature, but this is soon compensated for by the adjustment of the body mechanisms. However, when the patient is placed in a carbon dioxide bath, besides these minor adjustments, there is a distinct rise in the alveolar carbon dioxide tension. This rise can be measured while the patient is in the carbon dioxide water bath, and is evident for some time after the patient leaves the bath.

A comparison of the height of the mean curves of the alveolar carbon dioxide tension during carbon dioxide water baths shows the effect of the carbon dioxide in the air of the room (Table VI and Fig. 2). The patients, when breathing room air, showed a 1 per cent greater alveolar carbon dioxide change, and the return to resting alveolar tension was delayed. When the patient was breathing outdoor air, there was a tendency to return to the resting alveolar carbon dioxide tension soon after the bath (Fig. 1).

Carpenter and Lee[10] state: "It has frequently been shown that the carbon dioxide tension of the arterial blood and the carbon dioxide tension of the alveolar air run parallel in normal subjects and are nearly identical." Thus, the rise in alveolar carbon dioxide tension found in these studies indicates a rise also in the arterial carbon dioxide tension. Therefore, the absorption of carbon dioxide from the baths, which increases the arterial carbon dioxide tension, may explain some of the beneficial effects noted in patients with cardiac and vascular conditions after they have taken this type of treatment.

B. *Skin Temperature.*—The studies of skin temperature reported here were made to ascertain whether or not significant changes occur in the carbon dioxide bath, which, if present, would indicate dilatation of peripheral vessels. As a control, the subjects were always observed in a plain water bath at the same temperature as that used for the

4. Absorption of carbon dioxide through the skin. It is considered that this was actually the source of the excess carbon dioxide which was eliminated during the bath periods in the mineral water. In the course of a bath in this water there is a marked accumulation of carbon dioxide on the skin. The experimental observations of Hediger,[5] described above, indicate that carbon dioxide can pass through the skin.

These observations conform closely with those of Groedel and Wachter,[7] who made extensive studies of this question with the natural mineral water of Bad Nauheim, in Germany. The only difference between our data and those reported by these authors is that the increase in carbon dioxide elimination was not evident in the period of fifteen to thirty minutes after the carbon dioxide bath. Groedel and Wachter, on the other hand, found that the increase in elimination of carbon dioxide persisted from one to one and one-half hours after the bath. In our series, the changes in the amount of carbon dioxide eliminated, the rise in the respiratory quotient, and the increase of respiratory minute volume were all essentially of the same proportions as in their studies.

The changes observed in the respiratory quotient, with an elevation to 1.3, indicate without question that some extraneous source of carbon dioxide was present, because, if it were all due to food or tissue oxidation, a quotient above 1 would be impossible.

It is considered, therefore, that the evidence strongly supports the idea that the carbon dioxide eliminated during a mineral water bath is actually excess carbon dioxide which is absorbed from the bath through the skin and carried to the lungs by the blood stream. This could perfectly well explain the increased respiratory minute volume, for carbon dioxide is a well-known stimulant of the respiratory center.

D. *General Considerations.*—Justification for the extensive use of mineral water baths containing carbon dioxide in the program of treating disorders of the heart and circulation has frequently been questioned by thoughtful physicians. They say that the results are entirely due to mental and psychological factors. We think that the data presented in this communication, as well as other observations on the effects of these baths, as outlined previously by one of us,[13] show that they have a distinct and definite physiologic effect. Further studies are required, of course, to demonstrate the complete details of this effect. The observations presented in this paper are a step in that program, and are considered to be strong support for the theory that the effects produced by the use of these baths depend on the absorption of carbon dioxide through the skin.

Barach and Steiner[14] state: "Constriction of the capillary bed has been produced by acute alkalosis, and carbon dioxide administration has been followed by dilatation of these vessels." In the conclusion of their paper they point out that the addition of 2 to 3 per cent of carbon dioxide to a low oxygen mixture prevented the develop-

Four possible sources of the excess in carbon dioxide elimination during the periods when the patient was in the mineral water bath may be considered:

1. Increase in the oxidative metabolism throughout the body. The fact that there was no increase in the oxygen consumption during the periods in the mineral bath would rule out this possible source.

2. Release of carbon dioxide in the body. There is no evidence to show that the exposure of the body to a bath of this type produces any marked shift in the constituents in the blood other than carbon dioxide. It is well known that an increase of fixed acids in the circulating blood will result in an increase of ventilation, with the elimination of excess amounts of carbon dioxide. The fact that the subjects within a short time after the bath showed an essentially normal amount of carbon dioxide elimination is certainly evidence against a possibility of any marked change in the acid-base equilibrium of the blood.

3. Hyperventilation. One must consider carefully whether the increase in respiratory minute volume is a possible cause of the excess elimination of carbon dioxide, or whether it is the result of a stimulation of the respiratory center by circulating blood which has acquired an additional amount of carbon dioxide from some outside source. It is well known that voluntary hyperventilation may result in the elimination of excess amounts of carbon dioxide.

Data obtained during the course of these observations showed that one subject increased the minute volume by 18 per cent in one period and over 50 per cent in another by voluntary forced breathing, which resulted in the elimination of approximately 25 to 28 per cent more carbon dioxide. This was associated with relatively little change in oxygen consumption. The respiratory effort required to carry on the forced ventilation resulted, in one period, in an increase of 8 per cent in the amount of oxygen absorbed. However, the percentage concentration of carbon dioxide in the expired air fell from 3.29 to 2.52 per cent. In all observations made with subjects in the mineral water the increased ventilation was accompanied by an actual increase in the concentration of carbon dioxide in the expired air.

A review of the data presented shows that an increase in the respiratory volume occurred only during the periods when the patient was in the mineral water bath. The increase in the carbon dioxide tension of the alveolar air when the subjects were in the carbon dioxide bath indicates also an increase of carbon dioxide in the arterial blood. Since the expired air during voluntary hyperventilation has a lowered concentration or percentage of carbon dioxide, and since an increased concentration was found uniformly in these studies, it appears that the increased minute volume is the result of a stimulation of the respiratory center by the circulating carbon dioxide, rather than the primary cause of the increased carbon dioxide elimination.

29.4° C. (85° F.) and 32.2° C. (90° F.) were used. When the baths were 35° C. (95° F.) and 37.8° C. (100° F.), the skin temperature was 0.5 to 1° C higher in the bath of carbon dioxide water.

5. A distinct hyperemia was noted over the immersed area of the skin when the patients emerged from the carbon dioxide water baths. This was noted at all the temperatures used, and was not present when the subject emerged from the plain water baths.

6. There was a marked increase in the elimination of carbon dioxide in the expired air during the time the patient was in the mineral water bath. This increase did not occur in the plain water bath.

7. No evident variation in the oxygen consumption occurred with either bath.

8. The respiratory quotient, therefore, showed a marked elevation when the patient was in the mineral water bath.

9. There was an increase in the respiratory minute volume during the mineral water bath which did not occur with the plain water bath. This increase was not as regular as that observed in the amount of carbon dioxide eliminated.

10. The possible source of the excess carbon dioxide is discussed. The evidence supports the theory that this extra carbon dioxide is obtained by absorption of the carbon dioxide in the water through the skin and its subsequent elimination through the lungs. Other possible causes of this excess elimination, such as increased metabolism, voluntary hyperventilation, and chemical changes in the blood other than in the carbon dioxide, were considered, but cannot be accepted as valid causes for the observations.

11. It is, therefore, concluded that the results obtained in the treatment of patients with carbon dioxide mineral water baths depend, in part, at least, on the absorption of carbon dioxide through the skin and its subsequent influence on the circulation and nervous system which occurs in the process of its natural elimination by way of the blood stream and the lungs.

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ment of clinical and electrocardiographic signs of coronary insufficiency when patients breathed the mixture. McDowell,[15] in studies on anesthetized dogs, found that the loss of tone caused by washing out the carbon dioxide does not affect all blood vessels alike. He concluded that the normal carbon dioxide content of the blood maintains a peripheral dilatation of the minute vessels, just as it maintains a central stimulation of the vasomotor center. Wolff and Lennox,[16] in studies of the pial vessels of trepanned cats, found that a decrease in the carbon dioxide content of the blood resulted in a moderate decrease in the diameter of pial arteries, whereas an increase in the carbon dioxide was followed by a marked increase in their size, and that dilatation was more readily produced than constriction.

In these observations each subject was his own control. In the first place, the base period on the day of the experiment was used to determine any changes resulting from the baths which followed. He also acted as his own control in that the changes resulting when he took a bath in plain water were compared with results obtained when the same patient took a bath in the mineral water. In addition, a preliminary training experiment was carried out with all subjects going through all the procedures except that no water was in the tub. Further, in two instances, additional check was made by preparing a plain water bath with the addition of salts which would bring the saline content to essentially the same level as that of the mineral water. These observations, we feel, eliminate the possibility that the salts in the water cause the variations observed. When the patients breathed only outside air during the experiments, all influence of carbon dioxide in the air over the bath was eliminated. It is, therefore, concluded that the significant changes observed in these studies are primarily due to the absorption of carbon dioxide from the mineral water through the skin.

SUMMARY AND CONCLUSIONS

1. Many observations have been made on the changes which occur in the alveolar carbon dioxide tension, the skin temperature, and the respiratory metabolism of human subjects who have been submerged in baths of either carbon dioxide water or plain water.

2. The aveolar carbon dioxide tension showed a 5 to 10 per cent rise during baths in the carbon dioxide water, and returned to the resting level about twenty minutes after the bath. There was no significant change during baths in plain water.

3. A comparison of the alveolar carbon dioxide changes during the carbon dioxide baths when the patient was breathing the air above the tub and when he breathed outdoor air indicates that the higher amount of carbon dioxide in the air above the tub caused a greater alveolar change by approximately one to two per cent.

4. There was no essential difference in the skin temperature during the carbon dioxide and plain water baths when bath temperatures of

ELECTROCARDIOGRAMS IN WHICH THE MAIN VENTRICULAR DEFLECTIONS ARE DIRECTED DOWNWARD IN THE STANDARD LEADS

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INTRODUCTION

THERE have recently appeared several papers describing electrocardiograms in which the main deflections in the three standard leads were downward, rather than upward.[1-5] Clinically, cases of this type have been found to fall into two groups: cases of right ventricular hypertrophy or dilatation,[3] and cases of severe myocardial damage.[2] The mechanism by which this pattern is produced, however, has not been well understood.

The problem can be partially resolved by theoretical analysis based on the fact that standard lead electrocardiograms are taken according to the following convention, arbitrarily established by Einthoven.[6] In Leads I and II, an upward deflection of the waves of the electrocardiogram will occur when the right arm is more negative (or less positive) than the left arm or left leg, respectively, and vice versa. In Lead III, an upward deflection of the waves of the electrocardiogram will occur if the left arm is more negative (or less positive) than the left leg, and vice versa. Since this is so, in a normal electrocardiogram in which QRS is upward in the three standard leads, the relations of the potentials of the extremities must be as follows:

In Lead I, the right arm is more negative (or less positive) than the left arm, or RA < LA.

In Lead II, the right arm is more negative (or less positive) than the left leg, or RA < LL.

In Lead III, the left arm is more negative (or less positive) than the left leg, or LA < LL.

Therefore, RA < LA < LL.

Using a similar analysis in a record in which QRS is downwardly deflected in the three standard leads, the following condition must hold:

In Lead I, the right arm must be less negative (or more positive) than the left arm, or RA > LA.

The eighth in a series of papers on the application of unipolar leads to the study of problems in electrocardiography.

Work done under the Martha M. Hall Foundation Fund for Research in Cardiovascular Disease, in memory of William Henry Hall.

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Received for publication March 13, 1944.

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left arm and left leg leads, but the right arm lead tends to be actually (+), and the left leg lead actually (−), in all records.

However, further examination of the right arm lead shows that the (+) deflection is of two forms: (a) a biphasic complex consisting of an initial downward deflection (Q) followed by an upstroke (R), and (b) a (+) deflection in which the initial and main deflection is an upstroke (R).

Examination of the left leg lead also shows two forms of the (−) deflection: (a) a biphasic complex consisting of a small initial upward deflection (r), followed by a deep S, and (b) a deep, initial, downward, main deflection (Q).

Examination of the left arm lead also shows two general types of patterns: (a) a biphasic complex consisting of an initial small upward deflection (r), followed by a deep S, and (b) an initial downward (Q) deflection.

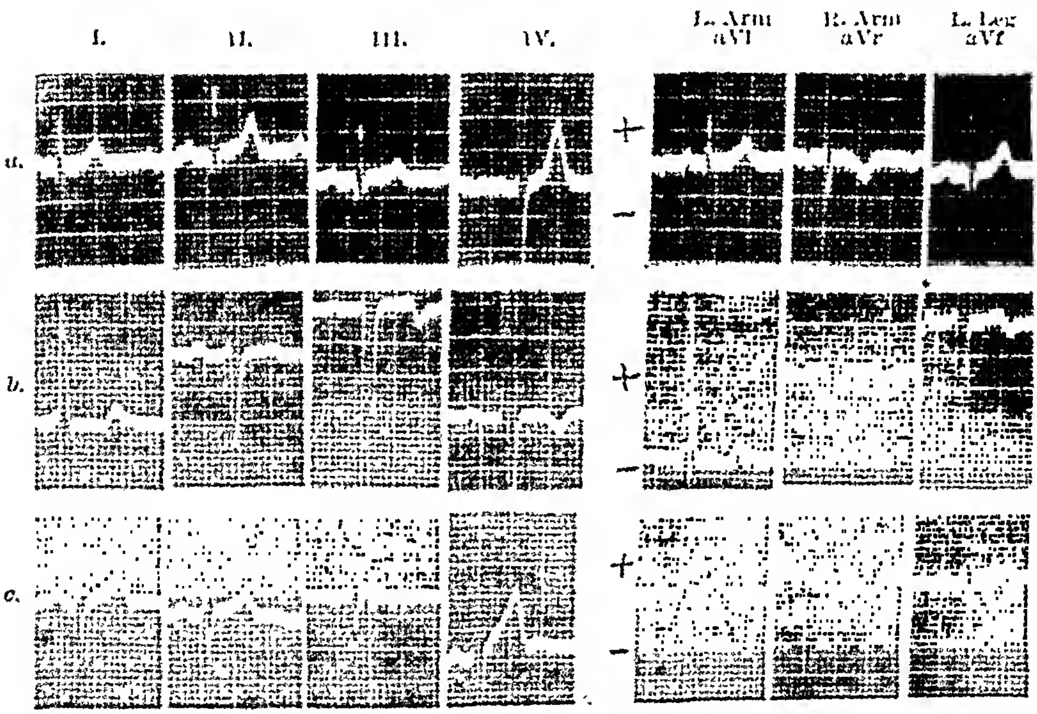

Fig. 1.—*a*, Normal. G. K., 41-year-old man. *b*, Marked left axis deviation. M. Z., 73-year-old man with hypertensive cardiovascular disease. *c*, Marked left axis deviation. R. H., 42-year-old man.

The interpretation of these patterns is as follows:

Right Arm Lead.—A. The biphasic QRS, as we have previously demonstrated, can be produced by both marked right axis deviation and marked left axis deviation.[8, 9]

B. The R type of deflection, as we have also shown, is found only in cases of extensive myocardial damage.[10*] This may occur with both anterior and posterior infarction. However, the exact degree of damage that must take place to cause this is not exactly known.

*See *Addendum.*

In Lead II, the right arm must be less negative (or more positive) than the left leg, or RA > LL.

In Lead III, the left arm must be less negative (or more positive) than the left leg, or LA > LL.

Therefore, RA > LA > LL.

In other words, in the normal record, the right arm potentials are relatively negative to those of the left arm and left leg, whereas, with downward deflections, a reversal of these conditions has taken place, and the right arm has become relatively positive to both the left arm and the left leg.

Fortunately, we are no longer limited to theoretical analysis of the possible potentials at the extremities, for, with a very simple technique, the actual unipolar extremity potentials can be recorded,[7] and the mechanisms which produce these changes can be more exactly studied.

MATERIAL AND METHOD

In a series of one thousand cases in which both standard leads and unipolar extremity leads were taken, there were fifteen in which the main deflections were downward in the three standard leads. In five of these, there was evidence of enlargement of the right ventricle, or of conditions in which right ventricular hypertrophy might be expected (chronic asthma and pulmonary tuberculosis). One of these patients died, and autopsy confirmed the diagnosis of right ventricular hypertrophy. The other ten were cases of myocardial infarction. In three of these, there was radiographic evidence of ventricular aneurysm.

In addition to these cases, we had the opportunity to study eight other autopsy cases, collected by one of us (S. P. S.), in which QRS pointed downward in the standard leads. One of these patients had multiple myocardial infarcts; the others had pulmonary tuberculosis and merely showed right ventricular hypertrophy or dilatation at autopsy.

Standard leads were taken as usual. For unipolar leads, the technique developed by one of us (E. G.)[7] of obtaining augmented unipolar extremity leads was used. The author's indifferent electrode of zero potential was used for the unipolar leads.[7] Some of the precordial leads were taken with the left leg as the indifferent electrode. The others were taken with the author's indifferent electrode.[7]

RESULTS

Fig. 1, *a*, shows the unipolar extremity leads of a normal subject, for comparison with the other records. Note that the right arm lead is negative (−); the left arm and left leg leads are positive (+).

The cases in which QRS was downwardly directed as a result of right ventricular hypertrophy are shown in Fig. 2, and those in which the cause was myocardial infarction, in Fig. 3. Fig. 2, *d*, is from a case of atypical right bundle branch block in which the QRS in the standard leads was directed downward.[5] This patient had anterior infarction.

On cursory examination, it will be noticed that, as was theoretically predicted, the right arm lead is not only relatively less negative than the

consisted in a shortening of the initial downward deflection and a decrease in the depth of the T wave. The left arm lead in Fig. 2, *c*, is, therefore, basically similar to the right arm lead. This does not occur in the cases of this type in which there is anterior infarction (Fig. 3, *a*, *b*, and *c*).

The explanation of this unusual condition is as follows: Normally, the heart lies obliquely, so that the right shoulder girdle and the right arm lead face the interior of the heart (the endocardium). Since the endocardium is (–) as the QRS is written, the right arm lead is also (–). When the heart is very vertical, the right arm lead only partially faces the endocardium, and its potential becomes biphasic (QR).* In such a case, the left arm lead also partially faces the endocardium, and its potential tends to resemble that of the right arm lead.[8, 9] Roentgenograms of this patient's chest confirmed the supposition that he should have a long, narrow heart.

In a case of anterior infarction, the downward deflection of the left arm lead is due to the fact that the left arm lead faces the epicardial surface of the ventricle which has been infarcted.[8]

We thus have the possible interaction of five different factors (left axis deviation, right axis deviation, marked myocardial damage, anterior infarction, posterior infarction) as a cause of these patterns.

Marked right axis deviation, alone, can cause a biphasic right arm lead, a downward left arm lead, usually consisting of an rS, and a downward left leg lead consisting usually of a biphasic rS. This combination will produce a downward deflection in the three standard leads (Fig. 2, *a*, *b*, and *c*).

Marked left axis deviation can cause the biphasic right arm lead and a downward left leg lead consisting of an rS, but the left arm lead is characteristically upward and usually very high. In such a case, Lead I will be tall, and only Leads II and III downward (Fig. 1, *b*). However, if anterior infarction occurs in such a case it will cause marked lowering of the left arm potentials because a Q wave results.[8] This will cause Lead I to point downward, also. Fig. 3, *c*, illustrates such a case. Here there was marked left axis deviation due to the presence of a large ventricular aneurysm, and a downward left arm lead as a result of the anterior infarction.

Extensive myocardial damage, either due to anterior or posterior infarction, results in a (+) right arm lead and a Q wave in the left arm or the left leg lead, depending on the location of the infarct. This alone is not sufficient to cause a downward QRS in the standard leads, unless both anterior and posterior infarction are present (Fig. 3, *a* and *b*). In such a case, there will usually be a Q wave in Leads I, II, and III.

Anterior infarction, alone, causes only a lowering of the left arm lead (due to the Q wave). Ordinarily, the right arm lead remains (–) and

*See *Addendum*.

Left Leg Lead.—A. The biphasic rS is regularly seen in left axis deviation.[8] We have demonstrated that it also occurs in cases of marked right axis deviation and right ventricular hypertrophy.[9]

B. The deep Q wave is characteristic of posterior infarction.[8, 11]

Left Arm Lead.—A. The biphasic rS is regularly seen in right axis deviation.[8]

B. The Q, with a "coronary," or coved, T wave, is characteristic of anterior infarction.[8, 11] The left arm lead of Fig. 2, *c*, from a case of right ventricular hypertrophy, superficially resembles this pattern.

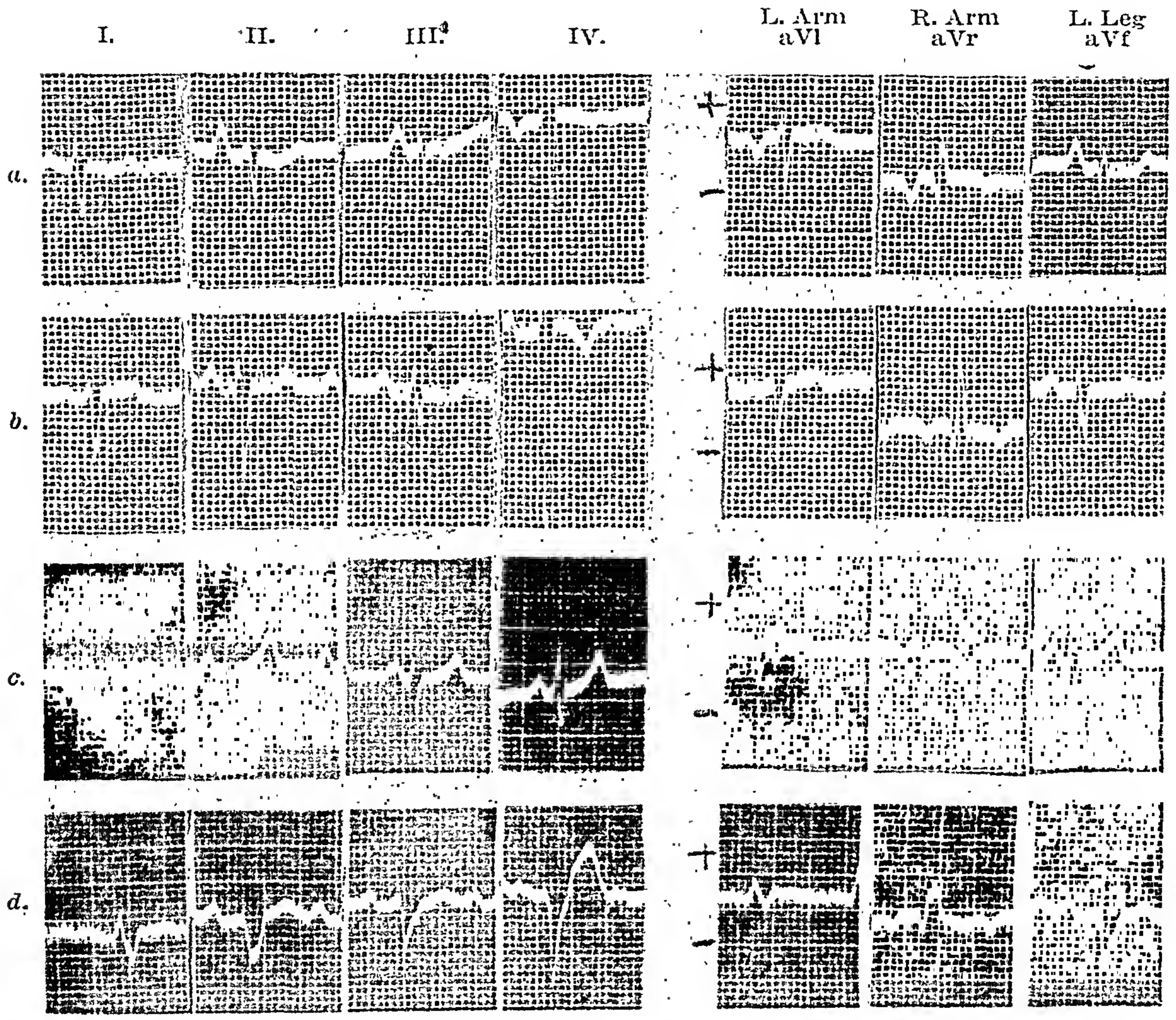

Fig. 2.—Downwardly deflected QRS in cases of right ventricular hypertrophy (*a*, *b*, and *c*). Fig. 2*d*, is from a case of atypical bundle branch block. It is not known whether right ventricular hypertrophy was present in this case. *a*, B. K., 59-year-old white man with chronic asthma and emphysema. The patient died, and autopsy revealed the greatly enlarged right ventricle. *b*, K. R., 63-year-old white man with chronic asthma. *c*, S. K., 61-year-old white man with chronic bronchitis and asthma. *d*, W. M., 45-year-old man. Arteriosclerotic heart disease, and anterior infarction.

Furthermore, a small Q_1 is present. A similar pattern was observed in two of our other cases in which there was only right ventricular hypertrophy at autopsy.[3] We made very careful studies of this case; over twenty unipolar leads were taken from all regions of the surface of the body, and there was a gradual transition from the pattern seen in the right arm lead to that seen in the left arm lead as the electrode moved across the upper portion of the body to the left. The change

In the case of atypical right bundle branch block (Fig. 2, *d*) there was a biphasic right arm lead, and the pattern may therefore be considered as also due, at least, in part, to marked axis deviation.

To summarize, a downward *QRS* in the three standard leads may occur as the result of: (1) Marked right axis deviation. This is usually due to right ventricular hypertrophy. (2) Anterior infarction in association with marked left axis deviation. (3) Posterior infarction in association with marked right axis deviation. (4) Extensive myocardial damage due to both anterior and posterior infarction.

DISCUSSION

It has been said[1] that downward deflection of *QRS* in the standard leads cannot be interpreted by the Einthoven triangle concept. A simple illustration will prove the fallacy of this:

Fig. 4 gives the range of potentials for each of the unipolar extremity leads. Normally, the electrical axis (at the instant the peak of the QRS complex is being written) lies in a range of 0° to +90°. Thus, if the electrical axis were +40° (point *A* in Fig. 4), it can be seen that the left arm lead would be (+), the right arm lead (−), and the left leg lead (+).

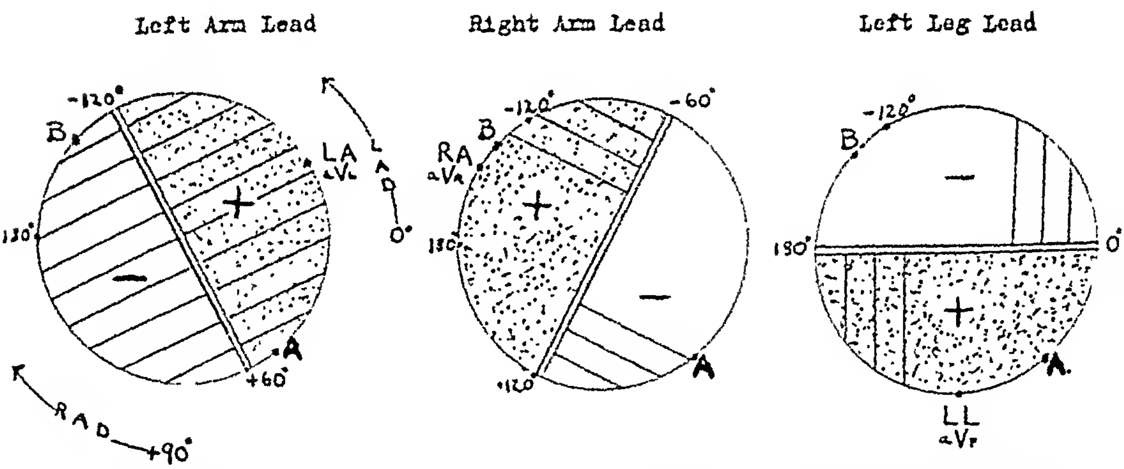

Fig. 4.—Graphs showing the relationships between the electrical axis and the polarities and potentials of the unipolar extremity leads. The diagonal and vertical lines indicate how the amplitudes of the records vary when the electrical axis changes.

which is normal. However, if the electrical axis were −130° (point *B* in Fig. 4), the left arm lead becomes (−), the right arm lead (+), and the left leg lead (−), (Fig. 4). In other words, cases in which there is a downward deflection in the three standard leads are merely examples of extreme degrees of axis deviation. From Fig. 4, one can see that the electrical axis of such records must fall within the range of −120° to 180°.

There is one more point to be discussed. It was pointed out above that marked right axis deviation, *without* myocardial infarction, can cause the downwardly deflected QRS. Study of Fig. 4 shows that the electrical axis in such a case must have rotated clockwise to reach at

the left leg lead (+). However, as was mentioned above, the addition of marked left axis deviation causes changes in the latter two leads, and a downward deflection in the standard leads results (Fig. 3, *c*).

Posterior infarction, alone, causes only a lowering of the left leg lead (due to the Q wave[8]). The right arm lead remains (−) and the left arm lead (+). Marked right axis deviation in such a case will cause a downward left arm lead and a biphasic right arm lead, and so produce a downward deflection in the standard leads. Fig. 3, *d,* approaches such a pattern.

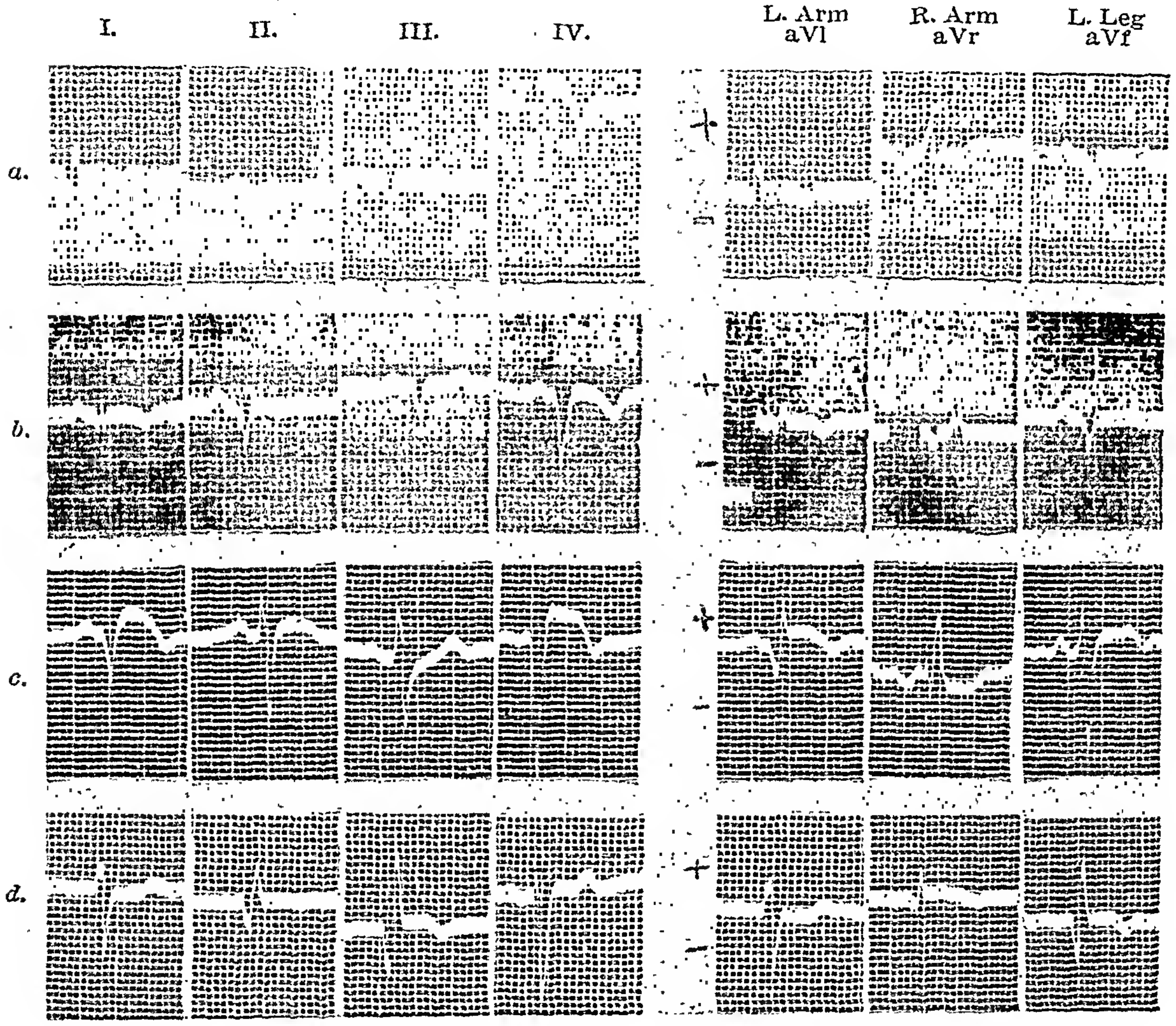

Fig. 3.—Downwardly deflected QRS in cases of myocardial infarction. *a,* B. Z., 55-year-old white man with signs of anterior and posterior myocardial infarctions. *b,* L. R., 53-year-old white woman with signs of anterior and posterior myocardial infarctions. *c,* C. H., 59-year-old white man with anterior infarction and marked left axis deviation due to aneurysm of the left ventricle. *d,* W. N., 54-year-old white man with posterior infarction and aneurysm of the left ventricle.

Combined anterior and posterior infarction produces a Q in both the left arm and left leg leads, but does not necessarily cause reversal of the normal (−) potential in the right arm lead, which is necessary to produce the downward deflection in the standard leads. When, as was pointed out above, the right arm becomes (+) because of the marked myocardial damage, the downward pattern in the standard leads occurs (Fig. 3, *a* and *b*). Theoretically, marked right or left axis deviation in a case of anterior and posterior infarction could also cause this pattern.

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ADDENDUM

Recent studies of ours, using multiple unipolar leads from the surface of the body in cases with a downward QRS, show that the biphasic QRS of the right arm lead can be explained by backward displacement of the apex of the heart, so that the right arm lead records potentials which are ordinarily found over the upper back. If this occurs in a markedly vertical normal heart, in addition to a biphasic right arm lead, the left leg will face the right ventricle, instead of the left ventricle, and will point downward, as will Leads I, II, and III.

Studies in cases in which the right arm lead has an initial main (+) deflection indicate that this may be due in part to forward displacement of the apex of the heart, so that the (+) right arm lead is similar to unipolar leads from the right upper chest and sternal regions. Although we had previously found this only in cases of infarction, we recently had one case of right ventricular hypertrophy in which this occurred.

least 180° (where the left leg lead becomes isoelectric again). Theoretically, therefore, the possibility exists that extreme left axis deviation, without myocardial infarction, might also be able to produce a downwardly deflected QRS. In such a case, the electrical axis would have to rotate counterclockwise to at least −120° (where the left arm lead becomes isoelectric again). Although we have not seen any unequivocal cases of this type, Fig. 1, *c*, illustrates a case of left axis deviation in which this tendency was present.

CONCLUSIONS

Normal and abnormal standard lead electrocardiograms ordinarily have the QRS in one or more leads directed upward. This is due to the fact that, although the range of the electrical axis of these records encompasses a wide area, it does not completely circle the 360°.

However, cases are occasionally observed in which the electrical axes do cover this range. Such cases fall into the following groups when studied with unipolar extremity leads: (1) Marked right axis deviation, usually due to right ventricular hypertrophy. In most of these cases there is an S wave in the three standard leads. Occasionally, a small Q_1 is observed in association with a small QRS_1. (2) Anterior infarction in association with marked left axis deviation. Standard leads show a deep Q_1 and a deep S_2 and S_3. (3) Posterior infarction in association with marked right axis deviation. Standard leads show the Q_2 and Q_3 which are characteristic of posterior infarction. (4) Combined anterior and posterior infarction. Standard leads show a Q_1, Q_2, and Q_3.

In these cases, the effect of axis deviation is particularly apparent in the unipolar extremity leads, especially the right arm lead. In the cases in which a shift in the long axis of the heart is responsible wholly, or in part, for the pattern, the right arm lead has a biphasic QR deflection.

In the cases in which extensive myocardial damage, and *not* any actual shift in the long axis of the heart, is responsible for the pattern, the right arm lead has a (+) R deflection.

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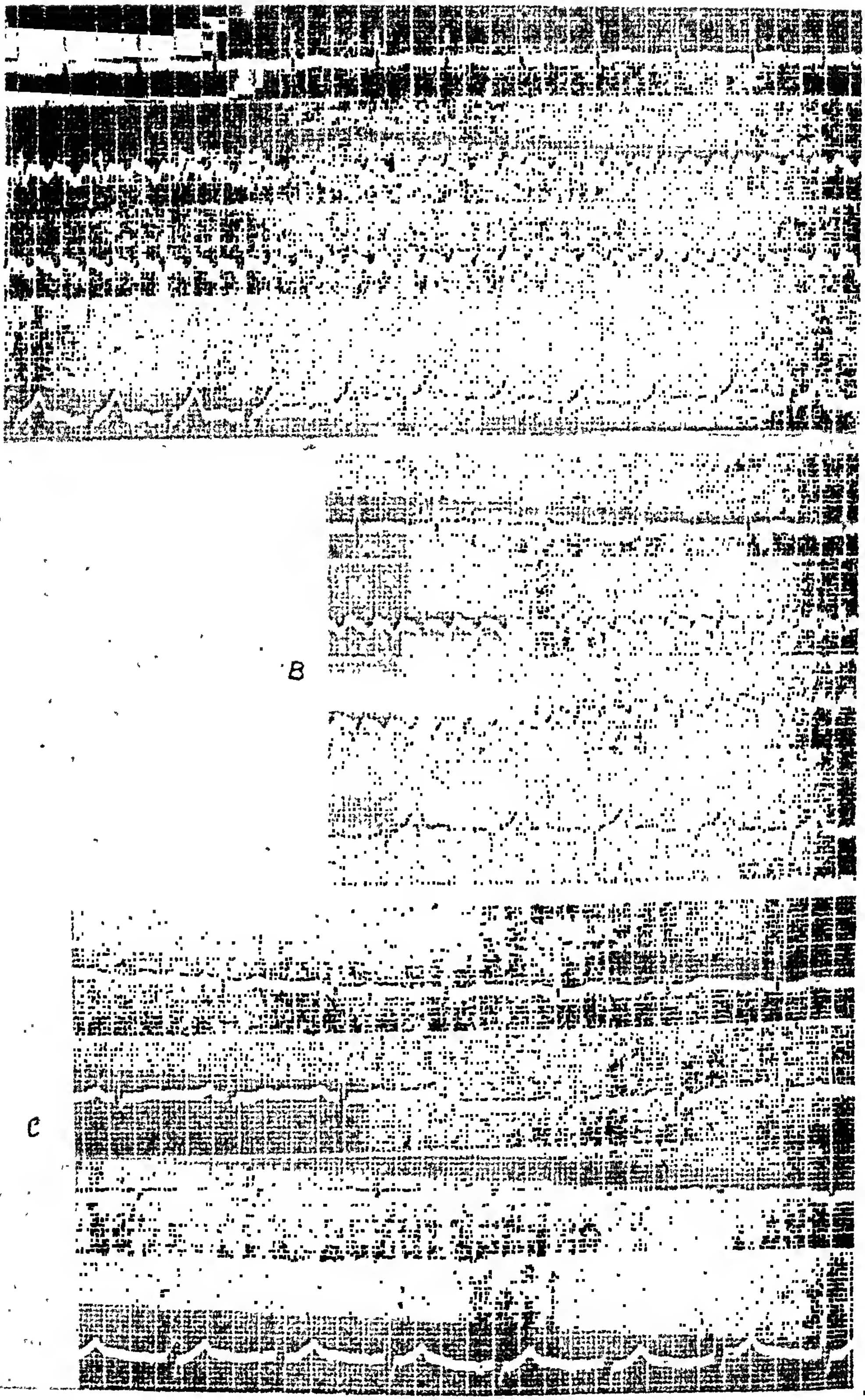

Fig. 1.—Lanatoside C in auricular flutter; Case 1. *A*, Four standard leads prior to administration of drug. Auricular rate, approximately 250 per minute. Ventricular rate, 100 per minute. *B*, Taken fifteen minutes after the administration of 1.6 mg. of lanatoside C intravenously. Auricular rate, approximately 250. Ventricular rate, 80. Slight sagging of S-T can be noted in Lead IVF. *C*, Taken two hours after administration of lanatoside C. Auricular rate, 70; ventricular rate, 70. Sagging of the S-T segment in Leads I, II, and IVF.

PROPHYLACTIC USE OF LANATOSIDE C IN AURICULAR PAROXYSMAL ARRHYTHMIAS

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INTRODUCTION

DIGITALIS preparations, particularly the most recently isolated glycosides, have been used for some time in the abortive treatment of the paroxysmal auricular arrhythmias.[1] Published accounts of this therapy pay little attention to the use of these digitalis bodies as a means of preventing frequent recurrences of these disturbing arrhythmias. This report is concerned, in the main, with this phase of therapy. Although the data presented are meager, the results obtained offer encouragement for further study.

The use of lanatoside C* orally in preference to other preparations of digitalis seems reasonable because this drug acts with rapidity, yet with minimal toxic effect, and retains its pharmacologic potency in vivo for at least twenty-four hours.[2, 3] The effect of this drug has been demonstrated both electrocardiographically and clinically[4] to be without variability, whereas other preparations of digitalis act with marked inconsistency.[5] Furthermore, the toxic effects of this drug, when administered over a prolonged period of time, are less than those of other digitalis preparations in common use.[6]

MECHANISM OF ACTION

Digitalis and its derivatives have a tendency to slow the rate of the heart in auricular paroxysmal arrhythmias, and often restore normal rhythm. The effect is not unlike vagal stimulation. Slowing of the heart rate without abolition of heterogenetic auricular activity, as demonstrated by the electrocardiogram (Figs. 1 and 2), may be noted either before the termination of an attack or as a fleeting change during the course of the arrhythmia. Digitalis acts directly on the heart muscle and indirectly by stimulating the vagus nerves. In the presence of auricular fibrillation and flutter, the increase in "circus rate" attributed to the action of this drug is apparently due to increased vagal tone, which shortens the refractory period of auricular muscle. The slowing effect on the ventricle is apparently due to both direct and indirect depression of conductivity in the atrioventricular node. In the presence of paroxysmal auricular tachycardia and flutter, the

From the Medical Wards of the Los Angeles General Hospital, College of Medical Evangelists' Division.
Received for publication March 20, 1944.
*Lanatoside C is marketed by Sandoz Chemical Works, Inc., under the name of Cedilanid.

effect of digitalis cannot very well be due to shortening of the refractory period of auricular muscle. Its effect must depend on its nodal action, or on some unknown action on the neuromuscular mechanism. It has been shown that digitalis acts upon auricular muscle by increasing its effective refractory period and by depressing its conductivity.[7-9] The abolition of a paroxysm of tachycardia or flutter cannot well be due to this action, for the indirect vagal action of the drug upon auricular muscle and the effects of digitalization and vagal stimulation in these arrhythmias are similar. Little is known regarding the action of digitalis on the rate of impulse formation in auricular muscle. It seems logical to assume, with the limited knowledge at our disposal, that digitalis abolishes these arrhythmias by exerting some effect on the nodal tissues.

Clinical observation has proved the usefulness of rapidly acting digitalis glycosides in the therapy of supraventricular arrhythmias, and, although their mode of action is still somewhat obscure, further clinical investigation offers the only method that will reveal the unknown physiologic factors. The frequency of recurrence of these arrhythmias is difficult to explain, but their appearance demands an efficient therapeutic investigation. It is hoped that this mode of therapy will receive more attention, and that the procedure herein briefly outlined will offer a basis for further study.

PROCEDURE

With the exception of one, those under observation were known to have had recurrent attacks of auricular paroxysmal tachycardia and flutter. This was confirmed electrocardiographically. The immediate attack received first consideration, and was treated by giving lanatoside C in a dose of 1.6 mg. intravenously. After cessation of the paroxysm, the drug was given orally, and the dose was determined by electroeardiographic criteria. It was felt that, when minimal sagging of the RS-T segment in one or more leads was present, there was adequate prophylactic saturation with the drug. This minimal effect on the electrocardiogram has been consistently demonstrated when lanatoside C has been administered.[9] It has been noted that, when this drug is given over a prolonged period of time in amounts in excess of that which produces the minimal electrocardiographic effect, premature ventricular contractions often produced disturbing symptoms. Each patient in this series was seen at least once every two weeks throughout the entire period of study. Careful historical data were gathered at each visit, particularly relative to untoward symptoms, produced either by the drug or by the recurrence of the arrhythmia. Those under observation were all ambulatory, and were allowed to carry on their normal environmental routines. In some, accessory medication was administered when necessary, and consisted, in the main, of mild sedatives such as the barbiturates or bromides.

RESULTS OF STUDY

Of the eight patients observed in this study, six had one or more paroxysms of auricular flutter, and two had frequent attacks of par-

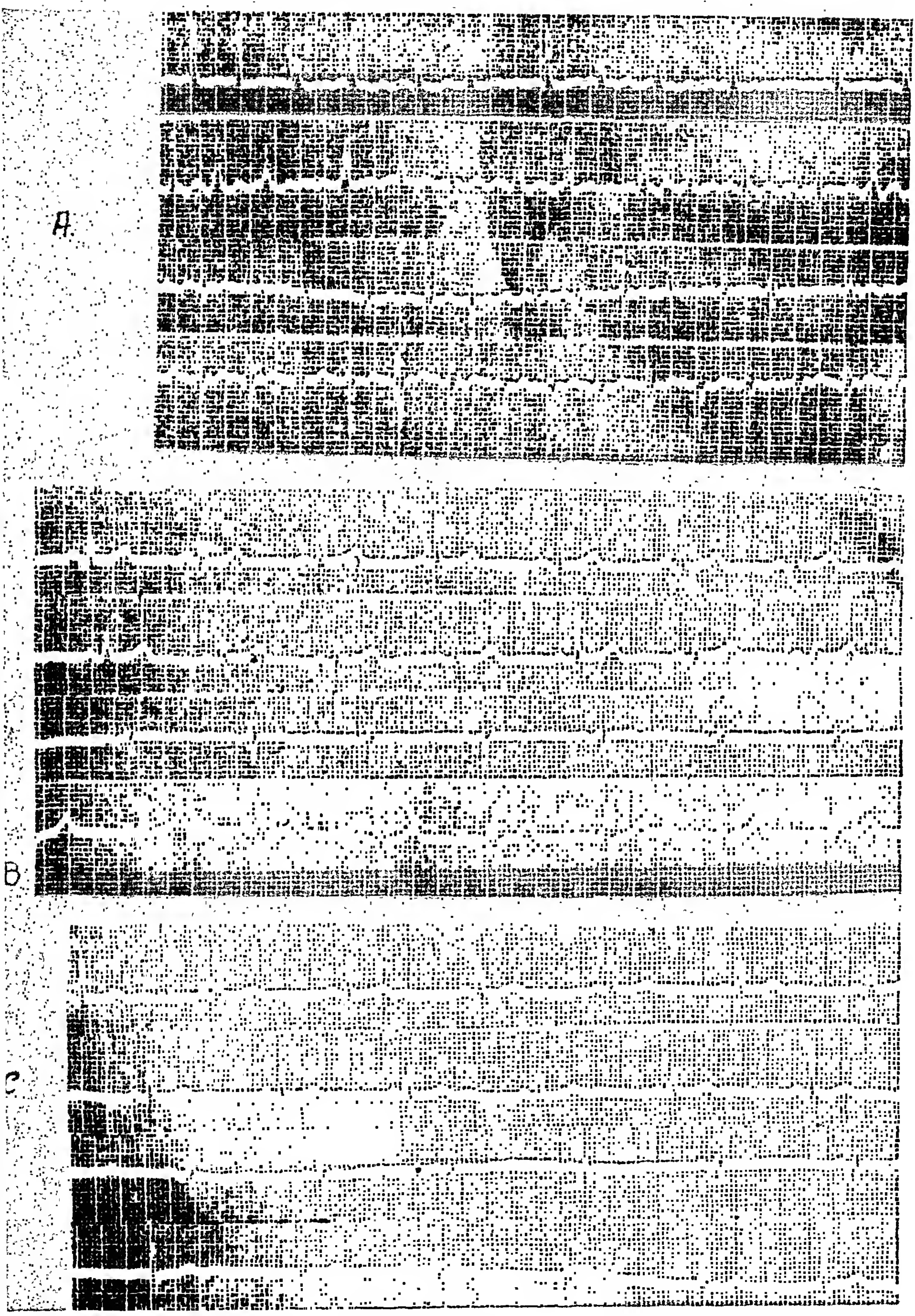

Fig. 2.—Lanatoside C in auricular flutter; Case 5. *A*, Taken prior to administration of drug. Auricular rate, approximately 250 per minute. Ventricular rate, approximately 122 per minute. *B*, Taken forty minutes after the administration of 1.6 mg. lanatoside C intravenously. Auricular rate, 62. Ventricular rate, 62 per minute. Note marked sinus effect with re-establishment of sinus rhythm. *C*, Taken six months after initial paroxysm. Patient receiving 0.5 mg. lanatoside C daily. Note minimal digitalis effect on the S-T segments.

oxysmal auricular tachycardia. With the exception of three, there was evidence of organic heart disease, and this, in the main, indicated coronary artery disease. One patient had rheumatic carditis. The average age was 50.3 years. Five were men; three were women. The average time of observation was approximately fifteen months. Each patient was seen during a paroxysm, and this paroxysm was treated with the full digitalizing dose of lanatoside C (1.6 mg.) intravenously; in one case the drug was given orally (6.5 mg.) over a period of forty-eight hours. Response to this medication, with re-establishment of normal sinus rhythm, occurred in all cases within a period of forty-eight hours. Immediately after the administration of the drug a primary ventricular slowing effect was noted (see electrocardiograms).

It is interesting that, prior to the lanatoside C medication, the entire group averaged 4.2 paroxysms in a twelve-month period. Maintenance therapy with lanatoside C over an average period of fifteen months reduced the incidence of recurrence to 0.37. The maintenance dose in all but one case did not exceed 0.5 mg. daily. Three of the patients had one recurrence of tachycardia during the period of observation. In one case a paroxysm followed an alcoholic debauch, in another it followed discontinuance of the drug for a period of one week, and in the third the arrhythmia made its appearance immediately after laparotomy for gall bladder disease. The recurrences in all three were of extremely short duration, and each abated without special medication.

The electrocardiographic effect of lanatoside C was observed in all of the cases, and this effect at no time abated until the drug was discontinued for a period of three days or more. This effect consisted of a slight sagging of the RS-T segment, with or without flattening of the T wave. In three instances, because of general apprehension, it was necessary to give 1½ grains of phenobarbital in divided doses. One patient received 30 grains of triple bromides daily, and two women, because of climacteric symptoms, received weekly injections of estrogenic substance. One patient, because of impending peripheral neuritis, received 30 mg. of thiamin daily.

The only untoward effect that could possibly be attributed to the use of this drug prophylactically was the occurrence of ventricular premature contractions in three cases.

SUMMARY

It appears that lanatoside C in some unknown way reduced the recurrence frequency of paroxysmal auricular tachycardia and flutter in eight cases from 4.2 in a twelve-month period to 0.37 in a fifteen-month period, following the use of the same drug in full digitalizing dosage at the onset of an initial paroxysm. The amount of drug used prophylactically did not exceed 0.5 mg. daily in seven cases; in the eighth the dosage was 1 mg. Electrocardiographic evidence of the effect of the drug on the RS-T segment and T wave was noted. Associated

TABLE I. PROPHYLACTIC USE OF LANATOSIDE C IN AURICULAR PAROXYSMAL ARRHYTHMIAS DATA ON CASES OBSERVED

NUMBER	DIAGNOSIS	AGE (YR.) SEX	ASSOCIATED CARDIAC DISEASE	PERIOD OF OBSERVATION (MO.)	DRUG TREATMENT OF PAROXYSMS	NUMBER OF PAROXYSMS IN 12 MONTHS PRIOR TO MEDICATION	NUMBER OF PAROXYSMS WHILE UNDER OBSERVATION	ACCESSORY MEDICATION	ECG EFFECT	UNTOWARD EFFECTS	DOSAGE MG. DAILY
1	Auricular flutter	51 M	0	8	1.6 mg. lanatoside C	6	0	Phenobarbital 1 grain daily	+	V.P.C.*	0.5
2	Auricular flutter	53 M	Coronary arteriosclerosis	14	1.6 mg. lanatoside C	4	1 Alcoholic debauch	Thiamin 30 mg. daily	+	0	0.5
3	Auricular paroxysmal tachycardia	62 M	Old anterior infarction	24	1.6 mg. lanatoside C	3	1 Discontinued drug 1 week	1½ grains phenobarbital daily	+	V.P.C.	0.5
4	Auricular paroxysmal tachycardia	32 F	0	5	6.5 mg. lanatoside C	8	1 Following laparotomy	2,000 R.U. estrogenic substance weekly	+	0	0.5
5	Auricular flutter	72 M	Coronary arteriosclerosis	14	1.6 mg. lanatoside C	6	0	Bromides 30 grains daily	+	0	0.5
6	Auricular flutter	49 F	0	30	1.6 mg. lanatoside C	4	0	2,000 R.U. estrogenic substance weekly	+	0	0.5
7	Auricular flutter	32 F	Rheumatic mitral and aortic endocarditis	32	1.6 mg. lanatoside C	3	0	Phenobarbital 1 grain daily	+	V.P.C.	0.5
8	Auricular flutter	52 M	Coronary arteriosclerosis	4	1.6 mg. lanatoside C	0	0	0	+	0	1.0

Totals

DIAGNOSIS	AVERAGE AGE (YR.)	ASSOCIATED DISEASE	AVERAGE TIME OBSERVED	AVERAGE	AVERAGE	DRUGS	ECG	PROPHYLACTIC DOSAGE
Auricular flutter 6 Auricular paroxysmal tachycardia 2	50.3	None 3 Coronary arteriosclerosis 3 Old infarction 1 Rheumatic 1	15 Months	4.2	0.37	Phenobarbital 3 Bromides 1 Estrogenic substance 2 Thiamin 1	Sagging RS-T 7 Flat T_3 1 case	0.5 mg. daily 7 1 mg. daily 1 case

*V.P.C.=Ventricular premature contractions.

SOME OBSERVATIONS ON THE SYNDROME OF SHORT P-R INTERVAL WITH LONG QRS

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THE electrocardiographic pattern of a short P-R interval with long QRS has been well established, and many cases have been reported. It is the purpose of this article to review briefly the literature on the subject and add another case in which there were certain unusual features not heretofore described.

REVIEW OF LITERATURE

Although the first case was described by Wilson,[1] in 1915, the next in 1921, by Wedd,[2] and the third in 1929, by Hamburger,[3] credit for the first systematic study goes to Wolff, Parkinson, and White,[4] who collected and reported eleven cases and established the anomaly of short P-R intervals in association with prolonged and aberrant QRS complexes as a clinical entity. Their work stimulated interest over all the world, with the result that there has been a steady increase in the number of recorded cases since 1930. Pezzi[5] reported three cases in 1931; and Holzmann and Scherf[6] reported two in 1932. Wolferth and Wood[7] reported ten cases, and Sigler,[8] one case, in 1933; Roberts and Abramson[9] reported one case, Faxen,[10] one, and Tung,[11] five, in 1936; in the same year Cossio, Bereonsky, and Kreutzer[12] reviewed twenty-seven cases from the literature, added seven of their own, and analyzed the group statistically from the standpoint of age, sex, type of tachycardia, presence or absence of coincidental organic heart disease, and change to a normal electrocardiographic pattern. In 1937, Sprague[13] reported one case and Bishop[14] described another, summarizing to date the literature on the subject. Additional cases were reported by Pines[15] and Moia and Inchanspe,[16] in 1938; in 1940 by Hunter, Papp, and Parkinson,[17] again by Wolferth and Wood,[18] and also by Levine and Beeson,[19] in 1941; in 1942 and 1943 one case was reported by Dassen,[20] one by Fox, Travell, and Molofsky,[21] one by Wood, Wolferth, and Geckeler,[22] and another by Clagett.[23]

In the first case, reported by Wilson,[1] that of a man, aged 23 years with attacks of paroxysmal tachycardia for eleven years, the characteristic electrocardiographic abnormality appeared on stimulation of the vagus nerve, and, when spontaneously present, could be abolished by the administration of atropine. A somewhat similar electrocardiographic anomaly was reported by Wedd,[2] and apparently also by Hamburger.[3]

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Received for publication March 21, 1944.

cardiac lesions in no way altered the result. The only untoward effect was the appearance, from time to time, of ventricular premature contractions. In three instances one paroxysm occurred recurrently, and in each of these a definite causative factor was established. The results obtained constitute evidence of the value of this drug for prophylactic therapy in cases of paroxysmal auricular tachycardia and flutter.

CONCLUSIONS

1. Lanatoside C appears to be of value prophylactically in the treatment of paroxysmal auricular tachycardia and flutter, provided the therapy is commenced by giving it intravenously to stop a paroxysm.
2. The effective prophylactic dose varied from 0.5 to 1 mg. daily.
3. Characteristic electrocardiographic changes may be used as a criterion of the effect of the drug.
4. Lanatoside C, because of properties discussed in this article, may be considered preferable to other digitalis preparations for prophylactic therapy.

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second, third, and fourth decades. Not infrequently the history dates back to puberty or earlier, when the patient first began to experience periodic attacks of palpitation. However, in a number of cases palpitation was never experienced. Among the arrhythmias which these persons are so prone to develop, paroxysmal auricular tachycardia ranks first; auricular fibrillation occurs considerably less frequently. Lately a few cases in which there were paroxysms of ventricular tachycardia have been described.[19] During the attacks of tachycardia of supraventricular origin the electrocardiogram invariably shows normal QRS complexes (except in the case here reported, which is the only exception so far observed).

The data on the effects of atropine and exercise are conflicting. Although in some cases these methods of vagus inhibition abolish the electrocardiographic abnormality, this is not universal. Similarly, the effect of digitalis is not constant.

Although there are a few cases in which organic heart disease was present, the type of organic involvement was quite diverse, and the organic heart disease, when encountered, was probably purely coincidental.

The fact that the syndrome is most frequently found in young persons, and that there are some cases in which reversal to the normal electrocardiographic pattern has been observed with advancing age—as in Case 9 of Wolferth and Wood[7] and Cases 3 and 8 of Wolff, Parkinson, and White[4]—suggests that certain persons may "outgrow" their electrocardiographic anomalies, i.e., the mechanism responsible for the short P-R interval and aberrant QRS complex becomes, for some unknown reason, less capable of functioning with advancing years.

The abundance of reported cases is paralleled only by a propensity to expound the various theories which have been advanced to explain the electrocardiographic anomaly. No attempt will be made here to discuss all these hypotheses, inasmuch as excellent reviews of the subject have already appeared.[7, 17, 18] Only two views will be briefly discussed, one because of its historical interest (Wolff, Parkinson, and White), and the other (Wolferth and Wood) because it appears to have established the explanation of the syndrome on a more sound basis both experimentally and clinically. The case presented here is analyzed in the light of the latter theory.

Wolff, Parkinson, and White,[4] who have the credit for the first systematic study of this electrocardiographic anomaly, believed that the phenomenon was one of regular sinus rhythm with functional intraventricular block. The latter was thought to be a vagal effect induced by excess vagal tone, slowing conduction through the bundle or one of its branches. They held the view that the syndrome was a vagal effect, for, in their cases, reversal to the normal electrocardiographic pattern took place on suppression of the vagal influence by exercise or atropine. In addition, in one of their cases the abnormal electrocardiogram could

In the latter case, that of a child aged $4\frac{1}{2}$ years who had an acute febrile illness, the author assumed that the bundle branch block occurred as the result of the respiratory infection, and the short P-R interval was interpreted as part of a nodal tachycardia.

Thus the original observation by Wilson remained unnoticed for a period of fifteen years, until 1930, when Wolff, Parkinson, and White[4] made similar observations. In the group of cases presented by these authors the following characteristics were noted: (1) The patients were usually young, healthy persons without evidence of organic heart disease, except for two cases in which organic heart disease was considered as purely coincidental. (2) Their electrocardiograms showed short P-R intervals (0.1 second or less) and ventricular complexes with certain characteristics suggesting bundle branch block (the QRS complexes were widened and slurred and the T waves might be opposite in direction from the main deflection of QRS). (3) In some cases both the P-R interval and the ventricular complex suddenly reverted to normal without change in contour or direction of the P waves. This might occur spontaneously or when the heart rate was increased by exercise or by atropine administration. When the heart rate slowed the abnormal characteristics might return. Vagal stimulation effected a return of aberrant complexes in one case. (4) Patients in this group were particularly liable to attacks of paroxysmal supraventricular tachycardia, during which the ventricular complexes invariably assumed a normal configuration. Thus, a syndrome of short P-R interval with long QRS became established as a clinical entity.

In the group of cases studied by Wolferth and Wood,[7] the following additional features were stressed: (1) The time from the beginning of the P wave to the end of the QRS complex was well within normal limits, despite the aberration of the ventricular complex. (2) If the P-R interval lengthened, the QRS complex simultaneously shortened to an equal extent. Consequently, in a given case the period from the beginning of P to the end of QRS remained substantially the same throughout, whether the electrocardiogram was normal or abnormal.

In addition to atropine, quinidine was found by Roberts and Abramson[9] to change the contour of their patient's electrocardiogram from abnormal to normal, and a somewhat similar effect was produced in one of the cases reported by Scherf and Schonbrunner[24] by the administration of large doses of digitalis, which caused disappearance of the abnormal QRS complex. On the contrary, digitalis uniformly produced further prolongation of the abnormal QRS in the case studied by Fox, Travell, and Molofsky.[21] Finally, Hunter, Papp, and Parkinson reported cases in which the QRS complexes were intermediate in shape between the normal and the aberrantly long QRS complexes.

This syndrome usually occurs in young persons, and is more common in males than in females. It has been found in persons of all ages (from early childhood to the seventh decade), but most frequently in the

(2) The premature invasion of a certain section of the ventricular muscle by this impulse causes a lengthening of the QRS complex at the expense of the P-R interval. (3) In some cases conductivity in the aberrant bundle may not be highly developed. Consequently, when impulses bombard it at a rapid rate, as during paroxysmal tachycardia, it may fail to function. This seems to offer an explanation for the transition from abnormal to normal complexes which is usually observed during the periods of supraventricular tachycardia. (4) Since Kent showed in rats that retrograde conduction was possible through the "right lateral bundle," therefore, "under certain circumstances a retrograde impulse in these individuals might travel from ventricle to auricle at a time when the physiological state of the auricular muscle would favor the inception of an abnormal rhythm." Thus the mechanism of production of arrhythmias as a part of the syndrome was explained. (5) In their cases the authors observed that, with change from the short P-R interval and long QRS complex to a normal P-R interval and QRS complex the duration of the interval from the beginning of the P wave to the end of the QRS complex tended to remain constant. On the basis of their theory the interpretation of this particular observation would be dependent on the fact that, since conduction through the junctional tissues (the node of Tawara and the bundle of His) is not interfered with the variable factor of early aberrant conduction from auricles to ventricles would be responsible for alteration in the duration and form of the initial portion of the ventricular complex in direct correspondence with the prematurity of arrival of the aberrant impulse in the ventricular muscle. (6) If early transmission of the impulse by way of Kent's bundle is responsible for this syndrome, there should be definite asynchronism in the contraction of the two ventricles. Evidence of such asynchronism the authors find in the electrocardiograms (aberrant slurred, long QRS complexes), in the marked reduplication of the first heart sound which was noted in two of their cases, and in the study of jugular phlebograms. Although at first they held that the right ventricle was the first to be activated,[7] in conformance with the anatomic observations of Kent, later[18] the authors conceded that in some cases the left ventricle could be activated first. This might necessitate revision of ideas concerning the anatomic location or locations of the aberrant pathway.

The theory of Wolferth and Wood finds support in recent observations of both anatomic and physiologic nature. Glomset and Glomset[28] maintained that they were able to demonstrate accessory neuromuscular connections between the auricles and ventricles, and the hypothesis of aberrant auricular conduction found experimental support in the work of Butterworth[29] and Butterworth and Poindexter,[30] who short-circuited the normal conduction system through an amplifier and produced ventricular asynchronism with the electrocardiographic picture of short P-R interval and long QRS. At the same time, reversal of transmission

be reproduced by vagal stimulation, and thus they repeated the original observation made by Wilson in 1915. However, in cases reported by other workers, the effect of vagal release on the electrocardiogram with a short P-R interval and long QRS has not always been the same. Besides, this hypothesis would imply a "paradoxical effect" of vagus tone, with the simultaneous exercise of two diametrically opposed influences, one accelerating conduction between auricles and ventricles, resulting in shortening of the P-R interval, the other retarding conduction through the bundle of His in the ventricles, giving rise to the lengthening and aberrant configuration of the QRS complex. The theory also implies that the vagus nerve may influence intraventricular conduction. Changes in the ventricular complex during stimulation of the vagus nerve in dogs were produced by Hering,[25] but they were in the amplitude, not the duration, of the QRS complex. Ritchie[26] similarly found that, in human subjects, stimulation of the vagus nerve did not effect any change in the duration of the QRS complex.

Wolferth and Wood[7] presented ten cases, in none of which did "vagal release" with atropine cause reversal to a normal electrocardiogram. Neither did vagus stimulation lead to return of the abnormality in the case in which spontanoeus restoration of the normal P-R interval and QRS complex occurred. These observations, in conjunction with certain other considerations, discredited the theory of Wolff, Parkinson, and White, and started these authors on a search for a different explanation. They postulated that there was some aberrant conduction bundle between the auricles and ventricles, and that it was able to transmit impulses. With this as a premise, they argued that the syndrome represented normal sinus rhythm, with conduction by a direct and shorter pathway between the sinus node and the ventricles, which resulted not in block or delay, but in an early arrival of the auricular impulse in the ventricular muscle. The abnormality was present when the impulses passed through this aberrant path, and the normal pattern was restored when the impulses returned to the normal pathway. They found support for their theory in the report of Kent,[27] who described a structure bridging the auriculoventricular groove at the right lateral border of the heart of the rat, connecting the right auricle and right ventricle, and subsequently referred to as the bundle of Kent. Lewis discredited the idea that any such bundle would be capable of transmitting impulses from auricle to ventricle, and the bundle of Kent temporarily fell into disrepute, only to be recently revived in this country by Wolferth and Wood, and independently in Germany by Holzmann and Scherf.[6]

Wolferth and Wood,[7, 18] firmly believe that the bundle of Kent or "some analogous structure" offers a satisfactory explanation of the phenomenon of short P-R interval and long QRS. They cite some rather convincing evidence in support of their view: (1) The shortness of the P-R interval is due to the short, direct pathway from auricle to ventricle.

Urinalysis showed the presence of 1 plus albumin and occasional casts. The hemoglobin was 14.6 grams. The leucocyte count was 12,550, with 65 per cent polymorphonuclear leucocytes. The blood serologic reactions were negative. A roentgenogram of the chest showed cardiac enlargement; the greatest transverse diameter of the cardiac silhouette measured 17.5 cm. inside the rib cage of 30.5 cm. There was a little mottled central lung density which was interpreted as evidence of passive congestion. The electrocardiogram is reproduced in Fig. 1.

Although clinically it was thought that the patient had auricular fibrillation with a ventricular rate of about 170, the electrocardiogram was at first interpreted as indicating ventricular tachycardia. It may be mentioned in passing that the tracing was examined hurriedly in the dark room immediately after developing. The patient received 30 grains of quinidine within a period of about eighteen hours, and the following morning was found to have regular rhythm with a rate of 80. Unfortunately, no electrocardiogram was taken at that time. A maintenance dose of 9 grains of the drug a day was administered without any

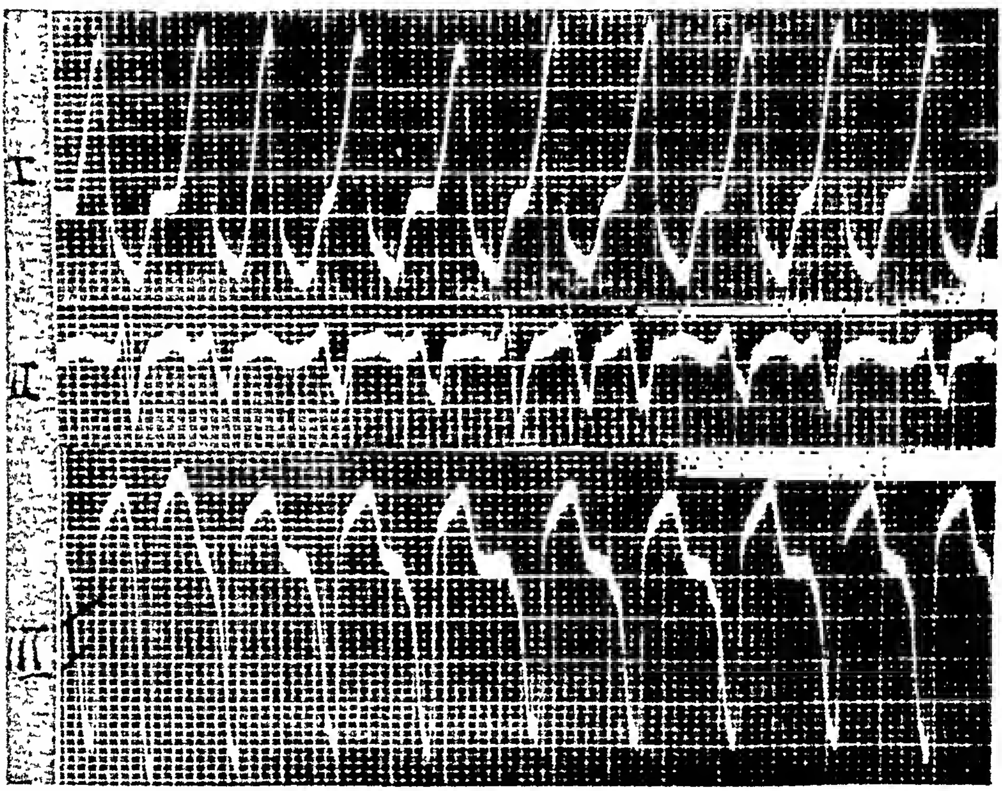

Fig. 1.—Electrocardiogram taken June 16, 1943.

change in rate or rhythm for several days. However, on June 23 the tachycardia recurred. The dose of quinidine was then increased to 24 grains a day, and, four days later, on June 26, the rhythm again became perfectly regular, with a rate of 70. The electrocardiogram (Fig. 2) on that day revealed regular sinus rhythm with a short P-R interval and aberrant QRS complex. In spite of a daily dose of 9 grains of quinidine, the tachycardia recurred once more on June 29. The tracing taken at that time was quite similar to the one taken on the day of admission. On re-examining the electrocardiograms it was found that the rhythm was

from ventricle to auricle caused typical auricular tachycardia, thus lending weight to the theory of Wolferth and Wood on the origin of paroxysmal tachycardia in this syndrome. Finally, in 1943, Wood, Wolferth, and Geckeler,[22] by anatomic examination of the heart of a child who had had this syndrome, were able to demonstrate an accessory bundle.

If we accept the aberrant pathway explanation, the demonstration that there is vagal influence in some cases may be interpreted to signify that, with increase in vagal tone, conduction through the normal junctional tissue is slowed or suppressed, and then proceeds through the aberrant bundle. With abolition of increased vagal tone in selected cases by means of exercise or atropine, conduction returns to the junctional tissue of the node of Tawara and the bundle of His. Wolferth and Wood thought that the vagus was a factor in determining whether or not the syndrome was present, depending on the influence of the vagus nerve on cardiac rate "so that if the cardiac rate were rapid the accessory tract might fail to conduct, whereas if it were slower this tract might be able under such circumstances to transmit an impulse."

REPORT OF CASE

W. A., a 57-year-old white American, a motor mechanic by occupation, was admitted to the hospital June 16, 1943, complaining of dyspnea. He had been in this hospital in 1941 for treatment of an upper respiratory tract infection, and stated that he left the hospital feeling well and continued in good health until about a year prior to this admission, when he first noticed dyspnea on lifting objects weighing up to 60 pounds. The exertional dyspnea became progressively more marked until, during the preceding few months, he would get breathless when he walked at a moderate pace on level ground. Three weeks prior to admission he had to give up his work and stayed around the house. He became subject to attacks of paroxysmal nocturnal dyspnea. A few days before admission he had a fainting spell not preceded by any aura and not accompanied by any convulsions, tongue biting, or loss of sphincter control. On the day of admission he went to a doctor who called his attention to the fact that his legs were swollen; he had failed to notice this himself. There was no history of any anginal pain. Except for the usual childhood diseases, he gave no history of any other serious illnesses. He stated that he had enjoyed good health all his life. He was operated on for a dislocated semilunar cartilage in the left knee in 1933. He denied venereal infection.

The patient was a well-developed, obese white man who was slightly dyspneic at rest and had some cyanosis. The heart borders could not be percussed because of the thick chest wall. The heart tones were of poor quality and distant. The heartbeat was rapid and irregular. No murmurs were heard. The radial pulse was of poor quality and irregular, with a pulse deficit of about 50. The radial arteries were not palpably thickened. The blood pressure was 130/90. There was dullness at the bases of both lungs, with some diminution in breath sounds, but without any râles. The liver was enlarged and slightly tender; its edge extended three to four fingerbreadths below the costal margin. There was moderate edema of both legs up to the knees.

really auricular fibrillation rather than ventricular tachycardia, and it was decided to digitalize the patient. Heavy doses of digitalis were administered, but, after the patient had received 39 grains of the drug in four days and was beginning to complain of nausea, a peculiar phenomenon was observed. The rhythm became even more irregular, as revealed by auscultation, and the electrocardiogram (Fig. 3) taken July 2 showed periods of ventricular asystole. It was thought that this might be due to the vagal effect of digitalis, and it was, therefore, decided (on July 3) to give the patient 20 minims of tincture of belladonna four times a day, in addition to digitalis. On July 5 the rate was found to be only about 54, with an irregular irregularity, and the electrocardiogram (Fig. 4) showed auricular fibrillation with a slow ventricular rate, but this time with a QRS which was normal in duration. In spite of continuation of the same therapy the rate returned again to what it was before the administration of belladonna, and the electrocardiogram closely resembled the one in Fig. 3. The patient complained of nausea and anorexia, and refused to eat or take any medicine. He left the hospital July 27 feeling better than he did on admission; the peripheral edema was entirely gone. He left against medical advice.

Fig. 1.—Electrocardiogram taken July 5, 1943.

The patient was readmitted Sept. 22, 1943, at which time he stated that after leaving the hospital the previous July he continued taking digitalis in doses of 1½ to 3 grains daily and felt "tolerably well" until three days before admission, when his dyspnea became more marked and he also noticed recurrence of swelling around the ankles.

It was observed that he had lost some weight, was somewhat dyspneic at rest, and had some cyanosis and slight pretibial edema. On auscultation of the heart the rhythm was found to be irregular, with an apical rate between 160 and 170 and a pulse deficit of 80. The edge of the liver could be felt about 6 finger breadths below the costal margin. The electrocardiogram was similar to the one in Fig. 1.

As it had already been observed that digitalis, even when pushed to the point of toxicity, was of no avail, it was decided to try another course of quinidine therapy. It was thought that possibly an insufficient amount of the latter drug was administered on the previous admission, and that the desired effect might be brought about with larger doses. This contention was well borne out by the subsequent course, for,

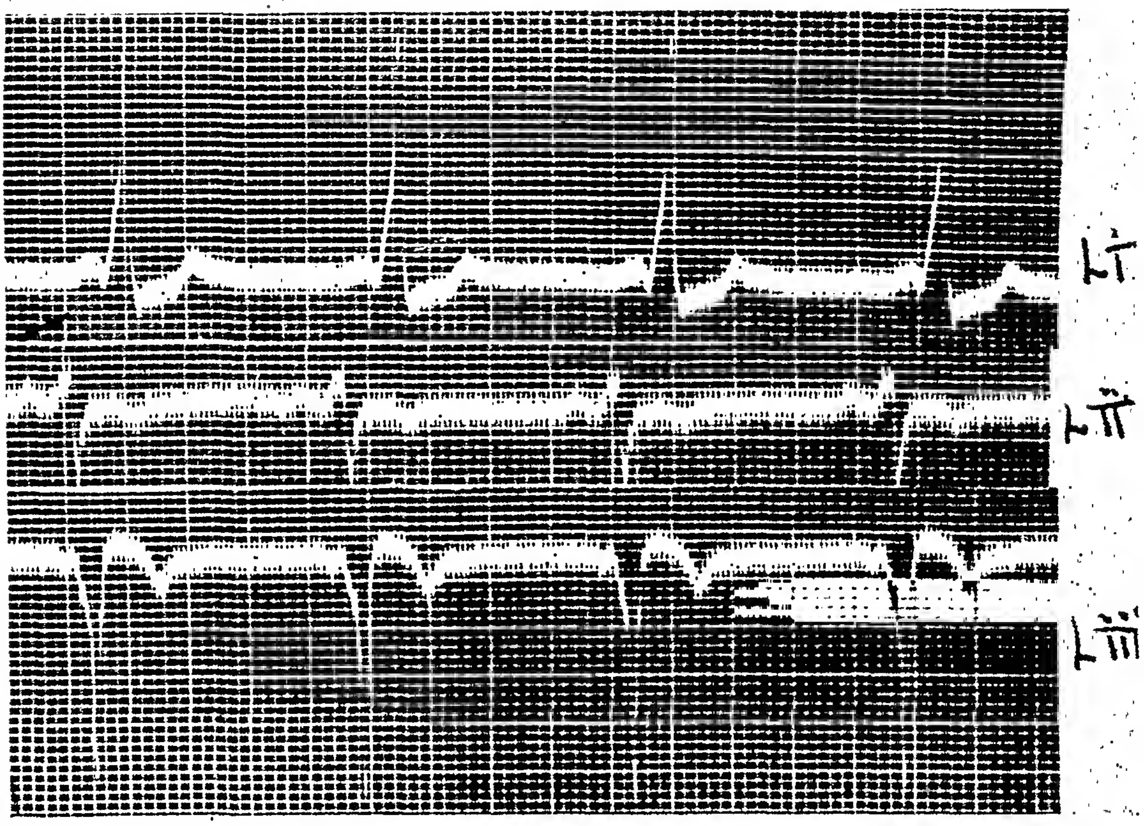

Fig. 2.—Electrocardiogram taken June 26, 1943.

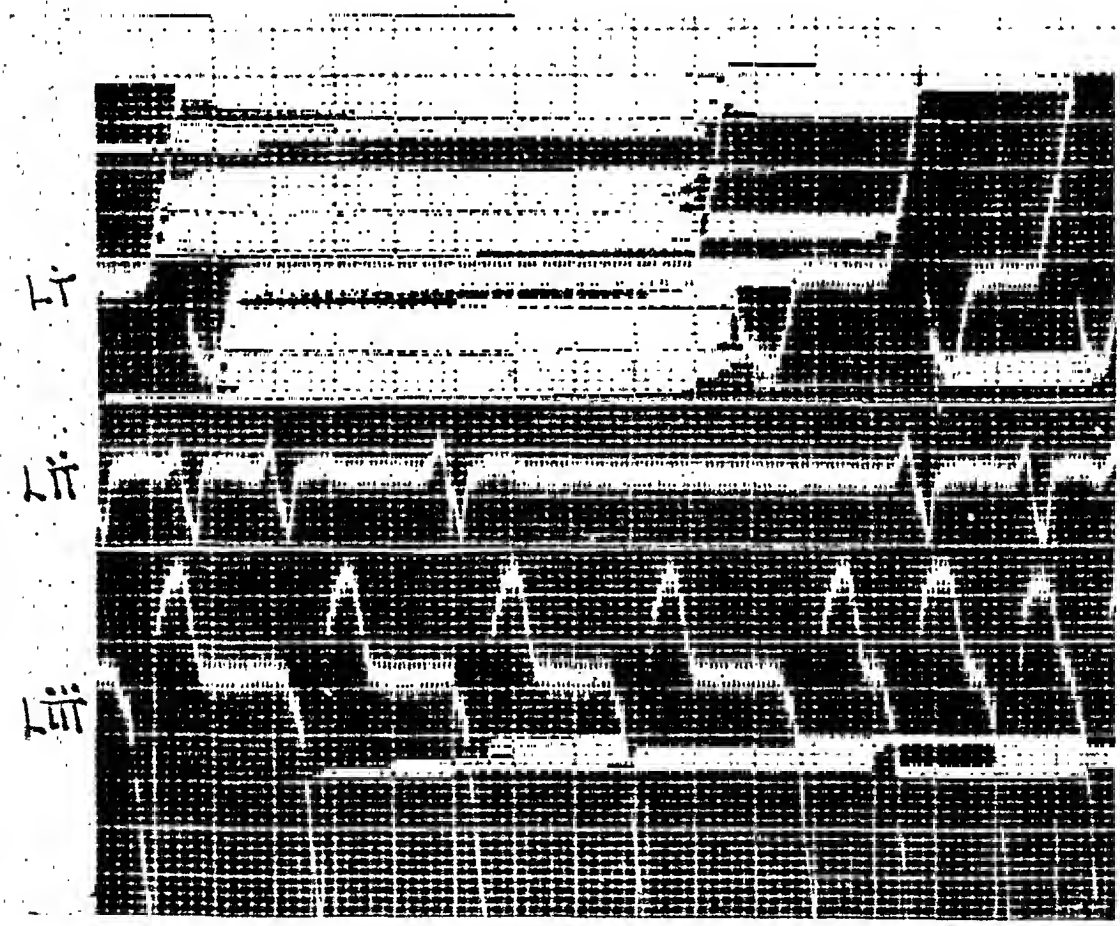

Fig. 3.—Electrocardiogram taken July 2, 1943.

was functioning. It is also interesting that, with the administration of tincture of belladonna in conjunction with digitalis for the purpose of eliminating the possible vagal effect of the latter drug, which was believed to be responsible for the short periods of complete A-V block with ventricular asystole (Fig. 3), the other possible effect of increased vagal tone, presumably responsible for the conduction of impulses through the aberrant bundle instead of the normal junctional tissue, seems to have also been abolished by belladonna, thus leading to the return of the QRS to normal (Fig. 4).

Although digitalization does not always slow the ventricular rate in all cases of auricular fibrillation, such slowing is practically the rule in cases of uncomplicated auricular fibrillation with congestive heart failure. This patient quite obviously had congestive failure, but digitalis in massive doses did not produce the expected results. Since the QRS complex during the tachycardia maintained its aberrant form, it may be concluded that, contrary to what is usual in other cases, in this instance the auricular impulses were conducted through the aberrant bundle. If this is true, the corollary would be that digitalis may be ineffective in slowing conduction through the abnormal pathway between the auricles and ventricles.

CONCLUSIONS

A consideration of the data in this case brings out two features: (1) The aberrant bundle may be able to conduct the auricular impulses during the periods of supraventricular tachycardia in cases of short P-R interval and long QRS complex, thus leading to preservation of the aberrant QRS complex during such attacks. (2) Digitalis may not exert any influence on the aberrant bundle, and the well-known effect of slowing of conduction through the normal junctional tissue by this drug may not be shared by the tissue of the abnormal pathway.

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after the administration of 54 grains of quinidine within the first twenty-four-hour period, regular rhythm was restored with a rate of 70 per minute. The electrocardiogram showed sinus rhythm with a short P-R interval and an aberrant, prolonged QRS; the tracing was quite similar to the one in Fig. 2. In the next twenty-four-hour period 24 grains of quinidine were given, followed from the third day on by a maintenance dose of 3 grains four times a day for five days, and then of 3 grains three times a day. When the dose was reduced to 3 grains twice a day, extrasystoles appeared. On resumption of the three times a day schedule for quinidine, uninterrupted sinus rhythm was readily restored and maintained indefinitely.

In addition, the patient was also given digitalis, for it was believed that his cardiac decompensation was not due exclusively to the tachycardia, but that there was also organic heart disease, presumably arteriosclerotic. There ensued a quite satisfactory and well sustained improvement. The patient felt fine, the greatest transverse diameter of the heart shadow decreased 2 cm., and all symptoms and signs of decompensation disappeared, with the exception of some hepatic enlargement. The latter was thought to be due to the irreversible changes of cardiac cirrhosis. The patient was discharged from the hospital Oct. 26, 1943. At home he continued taking 3 grains of quinidine three times a day and 1½ grains of digitalis daily. He returned twice, at monthly intervals, and his condition was found to be quite satisfactory; the rhythm was perfectly regular, with a rate of between 70 and 80.

COMMENT

This case presents certain interesting and rather unusual features. The underlying organic heart disease introduces a complicating factor in the consideration of the problem. It must be conceded that there is a possibility that the arrhythmia was secondary to heart disease and was independent of the electrocardiographic anomaly of short P-R interval and long QRS. However, there are reasons to believe that the arrhythmia was definitely related to the latter. With this as a premise, the unusual features observed in this case were: (1) preservation of the abnormally long and aberrant QRS during the period of arrhythmia, and (2) the response to digitalis therapy.

It will be recalled that, in previously reported cases, return of the QRS complex to normal with the onset of tachycardia of supraventricular origin was the rule. The invariable return of the aberrant QRS to normal is explained by the hypothesis that the anomalous conduction pathway may not be sufficiently developed to be able to convey the auricular impulses when they bombard it in rapid succession.[7] The case here presented constitutes an exception to that rule, for the QRS complexes retained their abnormal length and configuration during the periods of auricular fibrillation; in fact, the duration was longer then than at other times. This raises the question as to whether the entire excitation of the ventricles did not proceed by way of an accessory tract. The less likely alternative would be that left bundle branch block (functional) was present during the tachycardia, and that only the usual pathway

CONGENITAL HEART DISEASE: TRICUSPID ATRESIA AND MITRAL ATRESIA ASSOCIATED WITH TRANSPOSITION OF GREAT VESSELS

Report of Two Cases

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Atresia of the tricuspid or mitral valve is a rare abnormality of the heart. Maude Abbott[1] found twenty-five cases of tricuspid atresia in her analysis of 1,000 cases of congenital cardiac disease. Six other cases have been reported since that time, including two cases by Taussig,[2] in 1936, and one each by Brown,[3] in 1936, Roberts,[4] in 1937, Gibson and Clifton,[5] in 1938, Sakaki,[6] in 1938, Harris and Farber,[7] in 1939, and Holder and Pick,[8] in 1939, making a total of thirty-three cases in the literature. In 1939 Harris and Farber collected twenty-five cases of mitral atresia, and three further cases were reported by Gibson and Clifton,[5] in 1938, Walls,[9] in 1941, and Krumbhaar,[10] in 1942, making a total of twenty-eight cases. When these lesions are associated with transposition of the great vessels they present very interesting features clinically, anatomically, and embryologically.

We wish to report two cases, one of tricuspid atresia with pulmonary atresia and transposition of the aorta, and the other of mitral atresia with complete transposition of the great vessels. A search of the literature reveals no case in which there were the same combinations of anatomic defects as either of these.

REPORT OF CASES

Case 1.—Tricuspid and pulmonary atresia, with dextroposition of aorta and associated defects.

This white female, aged 7½ months, was born by an uncomplicated delivery on Sept. 17, 1940. Shortly after birth, cyanosis became evident and was present throughout life. At the age of 7 months she developed symptoms of a cold, with progressive cough and respiratory distress, and two weeks later, on April 30, 1941, she was brought to the Pediatric Out-patient Clinic of the Medical College of Virginia. Examination revealed dyspnea, cyanosis, and clubbing of the fingers and toes. There was slight injection of the pharynx and tonsils, and a few rhonchi were heard in both lungs. Her heart was enlarged to the left, but no murmurs were heard. The erythrocyte count was 6,430,000; the hemoglobin, 113 per cent; and the leucocyte count, 10,300, with 55 per cent polymorphonuclears and 45 per cent lymphocytes. A roentgenogram of the chest showed a moderately enlarged heart, with a cardiothoracic ratio of 51 per cent and a transverse diameter of the great vessels of 3.8

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Received for publication March 21, 1944.
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The left ventricle was greatly dilated and hypertrophied; its wall measured 6 mm. in thickness at the base. The interventricular septum was deflected obliquely to the right, and there was a defect in its base which measured 1 cm. in diameter. The right ventricle was small and aplastic; its cavity was little more than a narrow slit. Its wall measured 3 mm. in thickness. The aorta overrode the interventricular septal defect more to the right than to the left, so that it arose two-thirds from the right ventricle and one-third from the left ventricle. It was moderately dilated at its origin, where it measured 4 cm. in circumference. There were three aortic cusps, an anterior and a right and left posterior, with small fenestrations of each of the valve cusps. There were two coronary arteries; the left coronary arose from the sinus behind the left posterior cusp, and the right arose from behind the single anterior cusp. The aorta coursed upward normally and gave off its usual branches, including the ductus arteriosus, which was widely patent. Proximal to the ductus arteriosus the pulmonary artery became suddenly narrowed into a thin fibrous cord which did not reach the base of the heart, but disappeared 5 mm. from the right ventricle. Examination of the right ventricle failed to show any evidence of a pulmonary orifice.

Fig. 1 is a diagrammatic drawing which shows the essential features of the structure of this heart, and also demonstrates the course of blood flow through the heart. The complete anatomic diagnosis of the heart disease was as follows: (1) atresia of the tricuspid valve, (2) atresia of the pulmonary artery, (3) dextroposition of the aorta, (4) aplasia of the right ventricle, (5) hypertrophy of the left ventricle, (6) interauricular septal defect; persistent ostium secundum, (7) interventricular septal defect, (8) patent ductus arteriosus, and (9) fenestrations of aortic valve cusps.

DISCUSSION OF CASE 1

Tricuspid atresia is sometimes found as a single defect, but in the majority of cases there are many associated alterations in the architecture of the heart. Defects of the interatrial and interventricular septa, as well as hypoplasia or aplasia of the right ventricle, are almost constantly present, and transposition or pulmonary atresia is quite often associated with absence of the tricuspid valve. An interauricular communication is essential for the maintenance of blood flow, and the interventricular septal defect may be helpful in shunting blood into the pulmonary circulation in cases in which the pulmonary artery is patent. In cases in which the pulmonary artery is atretic, patency of the ductus arteriosus is necessary to bring blood into the pulmonary tree.

Cyanosis is explained by the admixture of arterial and venous blood (Lundsgaard's α factor), and by peripheral capillary stasis (Lundsgaard's D factor) which is incident to the increased back pressure on the venae cavae caused by the closure of the tricuspid orifice. The absence of murmurs in this case at first seems surprising, but may be readily explained. The only malformations in this heart which could be expected to produce a murmur were the patent ductus arteriosus and the interventricular septal defect, but since these openings were so large that they did not produce any obstruction to the blood flow, and since

centimeters. A preliminary diagnosis of congenital heart disease was made, and she was referred to the child cardiac clinic. However, the night before her appointment she developed severe respiratory distress, and the family physician was summoned. On his arrival the infant had ceased breathing, but he was able to revive her with mouth to mouth artificial respiration, and immediately sent her to the hospital emergency room. Examination there revealed the same abnormalities as before, plus extreme respiratory distress. Oxygen was administered without benefit, and she died two hours later. The clinical diagnosis was congenital heart disease with cardiac failure. Autopsy revealed, in addition to the cardiac abnormalities, pulmonary congestion and edema and passive congestion of the viscera. Microscopic examination of the heart showed fragmentation and vacuolization of the muscle fibers.

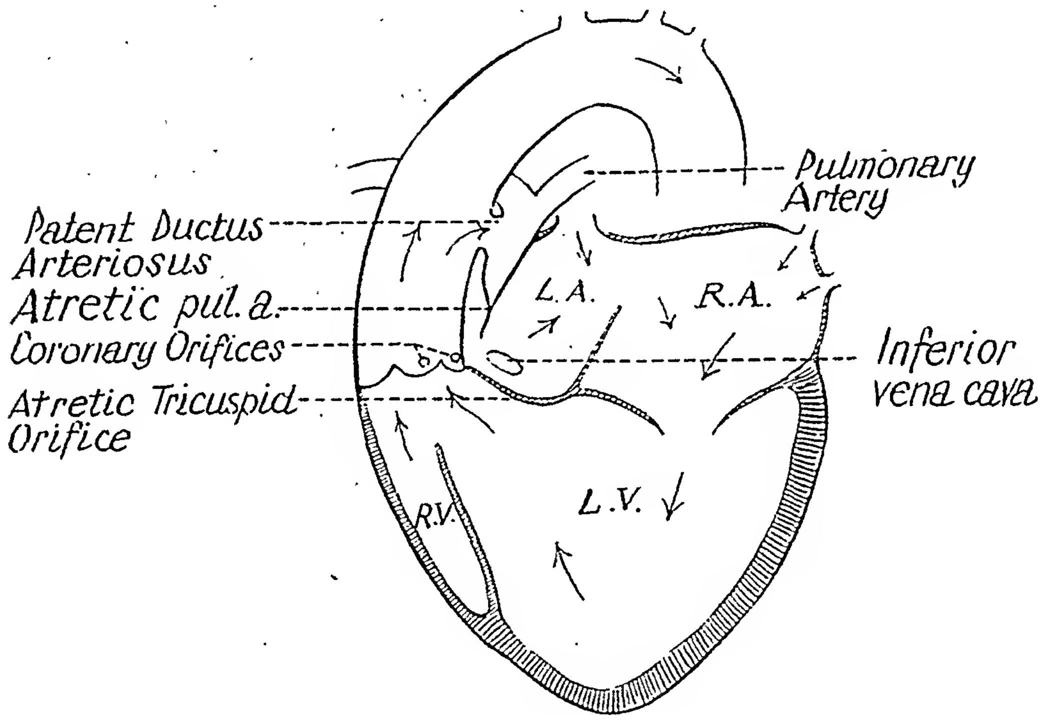

Fig. 1.

Gross Description of the Heart.—The heart weighed 45 grams and was obviously enlarged. Its apex was directed downward and to the left. The two auricles were of equal size; the right received the venae cavae and the coronary sinus, and the left received the pulmonary veins. The apex was formed by the left ventricle, which was greatly enlarged, and occupied three-fourths of the anterior surface of the heart, whereas the right ventricle was extremely small and flattened against the right side of the left ventricle.

The right auricle was normal in size and showed no appreciable hypertrophy. There was no evidence of a tricuspid valve; the floor of the auricle was completely closed by a smooth, slightly indented fibrous membrane. The only outlet of blood from the right auricle was through a defect in the upper part of the interatrial septum; this measured 1 cm. in diameter, and represented the ostium secundum of the septum primum. The septum secundum was not present. There were also numerous small perforations at the base of the septum which measured from 1 to 3 mm. in diameter. The left auricle was normal in size, and opened into the left ventricle through a normal, bicuspid mitral valve.

Farland[12] reported a case in which there was a rudimentary right-sided aorta, thereby substantiating an important link in Spitzer's theory. Spitzer's concepts are based on studies of phylogeny as well as ontogeny, and also emphasize the importance of torsion in the development of the heart and the influence of hemodynamics in producing this torsion and affecting the development of the cardiac septa. In the normal heart there is a 180-degree clockwise rotation of the conus arteriosus. If this rotation fails to occur the aorta will arise from the right side of the heart. Dextroposition of the aorta therefore results from a partial failure of this rotation and represents the first stage of detorsion. Spitzer interprets this right-sided aorta as a persistence or reopening of the right-sided aorta of reptilian hearts, rather than as an actual migration of the aorta from the left to the right ventricle. This misplacement of the aorta infringes upon the pulmonary artery, retarding its development and producing stenosis or atresia. An accompanying rotation of the valve cusps results in two posterior cusps and one anterior cusp. The left posterior cusp, from which the left coronary arises, corresponds to the normal left anterior cusp, and the single anterior cusp, from which the right coronary arises, corresponds to the normal right anterior cusp. The proper development of the individual cardiac septa depends upon their lying along the lines of force of the blood stream, so that when the direction of the blood stream is altered there is necessarily an alteration in their formation. In the case of the overriding aorta it is usually the septum aorticum and the upper part of the interventricular septum which suffer, thereby producing a defect in the base of the interventricular septum.

CASE 2.—Mitral atresia with complete transposition of great vessels and associated defects.

This colored female infant, weighing 5 pounds 10½ ounces, was born in the St. Philip Hospital of the Medical College of Virginia on Aug. 7, 1941. She was the thirteenth child of the family, and no history was obtained of congenital defects in the previous siblings. At birth a large umbilical hernia was present and slight cyanosis was noted. On physical examination the breath sounds and heart sounds were of good quality, and immediate operation was advised. Three hours after birth the hernia was repaired without difficulty under local novocaine anesthesia, and the infant appeared to be in good condition. Six hours later the cyanosis increased and she vomited her first feedings. Fluoroscopic examination of the chest revealed a moderately enlarged heart, with widening and pulsation of the mediastinum. The impression of the radiologist was congenital anomaly of the heart and aorta. Stimulants and fluids subcutaneously were given, but respiration became more difficult and the infant died thirty-five hours after operation. The clinical diagnosis was congenital anomaly of the heart and aorta, with pulmonary atelectasis. Autopsy revealed, in addition to the cardiac abnormalities, pulmonary edema and marked chronic passive congestion of the liver and lungs.

Gross Description of the Heart.—The heart was grossly enlarged, and there was moderate dilatation of both ventricles; the right ventricle was

there was no difference in the pressure on either side of these openings, no cardiac murmur was produced. In fact, the absence of murmurs is very helpful in the clinical diagnosis of tricuspid atresia, and Taussig[2] points out that the diagnosis can be definitely established when it is accompanied by pulmonary atresia and aplasia of the right ventricle. Persistent cyanosis with lack of cardiac murmurs narrows the field of differential diagnosis, roentgenologic studies demonstrate absence of the right ventricle, and the electrocardiogram shows left ventricular preponderance, thereby establishing the diagnosis. In addition, pulsation of the liver indicates that the foramen ovale is small and that the heart functions as a trilocular, rather than a bilocular, heart.

The mechanisms involved in the formation of this heart have many interesting aspects, some of which may be satisfactorily explained, but others we can only attempt to explain. The embryologic development of tricuspid atresia is sometimes ascribed to fetal endocarditis, especially when rudimentary and apparently fused valve leaflets are present, and when microscopic study reveals evidence of endocarditis. In this case, however, in which the valve was replaced by a smooth fibrous membrane, it seems more reasonable to consider it a true maldevelopment due to hypertrophy and resultant fusion of the fetal endocardial cushions which are the anlages of the valve leaflets. After this fusion occurred, there would be a constant flow of blood from the left to the right auricle which would prevent the closure of the interatrial defect, in this case the ostium secundum. Embryologically, the interatrial septum is first formed by the septum primum, which grows downward from the roof of the common auricle. The ostium primum is present as a defect in its base, but, as this becomes closed, the septum recedes from the roof of the auricles and the ostium secundum is formed. The septum secundum then forms along the right side of the primary septum, and a defect arises in its midportion which is known as the foramen ovale. The upper part of the septum primum acts as a flap for this foramen, and, after birth, fuses with it to form an intact interatrial septum. Therefore, if a defect is present in the midportion of the septum it should be considered a foramen ovale, if in the upper portion, the ostium secundum, and if in the lower portion, the ostium primum.

Transposition has been the most widely discussed congenital anomaly with respect to its embryologic formation, and is the most complicated and most difficult to explain. Harris and Farber[7] have reviewed the various theories, from that of Kurschner, in 1837, and Rokitansky, in 1875, to that of Spitzer in 1919 and 1921. More recently, Bremer[11] proposed a new theory based on the study of very early embryos. At present the explanations given by Spitzer are the most widely accepted and have received much support in recent literature. Harris and Farber[7] give a detailed account of Spitzer's views and report seventeen cases of transposition which support his theory. In 1941, Liebow and Me-

of mitral valve, (2) complete transposition of the aorta and pulmonary artery, (3) aplasia of left auricle, (4) defect in midportion of interventricular septum, (5) large defect in interauricular septum (patent foramen ovale), (6) hypertrophy and dilatation of right ventricle, (7) marked dilatation of right auricle, and (8) patent ductus arteriosus.

DISCUSSION OF CASE 2

Atresia of the mitral valve is frequently associated with other structural defects of the heart, most commonly with aplasia of the left ventricle and hypoplasia of the aorta, or with some form of transposition of the great vessels, usually dextroposition of the aorta. This case is unusual in that there was complete transposition of the aorta and pulmonary artery, with an aplastic left auricle and a relatively normal-sized left ventricle. The left ventricle received a considerable volume of blood through the large interventricular septal defect, and supplied this blood to the lungs through the pulmonary artery, so that its function was sufficient to allow it to develop in spite of the closure of the mitral valve. The tremendous dilatation of the right auricle was probably due to two factors. Some dilatation was undoubtedly caused by the increased volume of blood that it carried, as it was, in effect, the only functioning auricle, and this dilatation was exaggerated by the cardiac failure.

Although this heart falls in the group with cyanosis, cyanosis was not present at birth, and congenital heart disease was not suspected until the cyanosis developed postoperatively. Fluoroscopic examination showed evidence of some anomaly of the great vessels, but, since the left ventricle was not aplastic, the mitral atresia was not suspected. The cyanosis in this case was also contributed to by the $\propto$ and D factors of Lundsgaard and Van Slyke, as is true in most instances of cyanosis caused by congenital heart disease. This may have been exaggerated by interference with oxygenation of the blood in the lungs (Lundsgaard's 1 factor) due to the marked pulmonary congestion.

Harris and Farber[7] studied the question of transposition in association with mitral atresia, and postulated that there may be a causal relationship between the two. Of twenty-five cases of mitral atresia collected, they found that in fourteen there was also some form of transposition. In view of the rarity of both of these defects, and in view of the fact that mitral atresia does not occur in many cases of transposition, it is therefore probable that the mitral atresia in some way caused the transposition to occur. They adequately explained the usual dextroposition of the aorta by pointing out that, in accordance with Spitzer's theory, the diminished flow of blood to the left ventricle and the increased flow into the right ventricle would cause the left-sided aorta to become obliterated and the right-sided aorta to remain patent, thereby producing dextroposition or transposition of the aorta. They further state that the position and relative size of the aorta will depend

about twice the size of the left. There was marked dilatation of the right auricle, which was five times its normal size, whereas the left auricle was extremely small and aplastic. The right auricle received the venae cavae and the coronary sinus, and emptied into the right ventricle through a normal tricuspid valve. The left auricle was represented by a small slitlike pocket which communicated with the right auricle through a large defect in the central part of the interauricular septum. The left auricle received two normal-sized pulmonary veins, but did not communicate with the left ventricle. The usual location of the mitral valve was occupied by a smooth, somewhat indented fibrous membrane, with no evidence of a mitral valve or rudimentary valve leaflets. The myocardium of the left ventricle was normal in thickness, and that of the right ventricle was of the same thickness as that of the left. The two ventricles communicated through a large defect in the midportion of the interventricular septum. The aorta arose from the right ventricle and had three normal valve cusps, a single anterior cusp and a right and left posterior cusp. The coronary arteries arose from

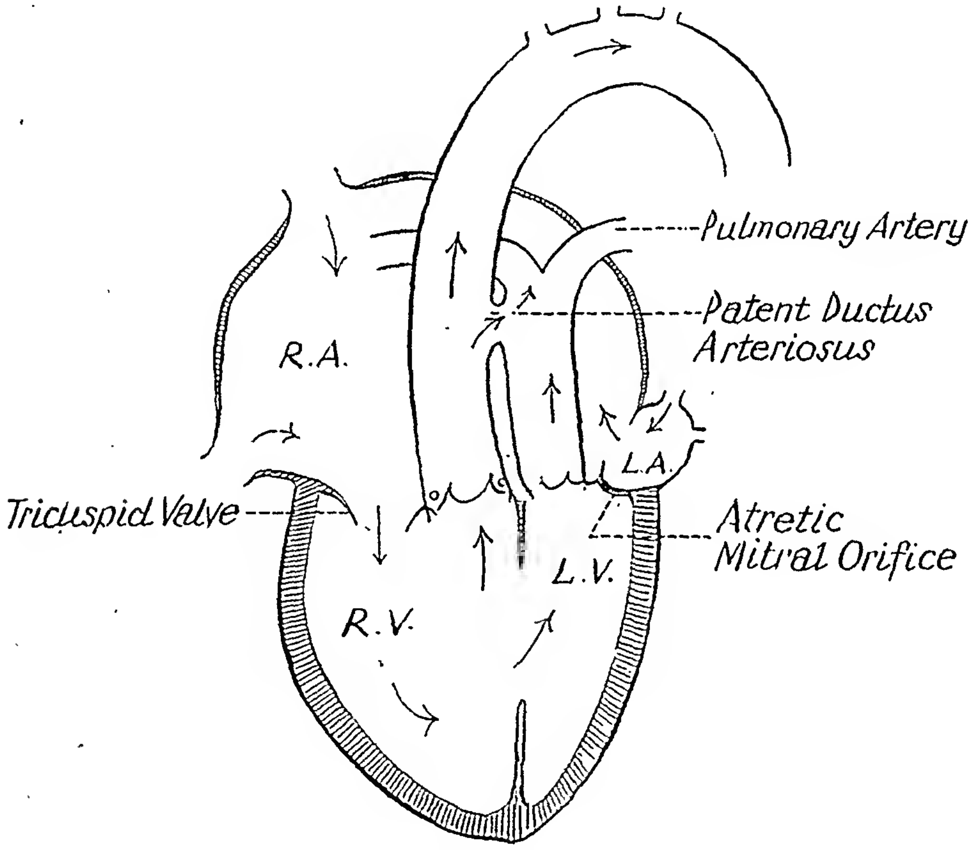

Fig. 2.

the sinuses behind the posterior cusps. The pulmonary artery arose from the left ventricle to the left of, and behind, the aorta, and it had three normal cusps. Both great vessels were of normal caliber and coursed upward in parallel. The ductus arteriosus was widely patent, and connected the aorta and pulmonary artery. Beyond the ductus arteriosus the pulmonary artery branched to supply each lung, and the aorta formed a normal left-sided arch which gave off its usual branches.

Fig. 2 represents diagrammatically the essential structural defects of this heart, and also demonstrates the probable course of circulation. The complete anatomic diagnosis of this heart was as follows: (1) atresia

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upon the time of development at which the mitral atresia takes place, and that, accordingly, four possibilities present themselves. If the atresia occurs before the obliteration of the right-sided aorta, a normal-sized or atretic dextroposed aorta will result, and if it occurs after the obliteration of the right-sided aorta, a normal-sized or atretic aorta in its normal position will be the result. All four of these varieties have been reported. In our case, however, in which there was complete transposition of both vessels, a different explanation is necessary to account for the fact that the pulmonary artery arose from the left ventricle. In studying this heart it is difficult to see how the atresia of the mitral valve could produce the complete transposition, or how the transposition could have any causal effects on the production of the atresia, for in this case neither lesion complemented the other. It therefore seems probable that the atresia and the transposition occurred independently, and that their association was merely coincidental. Transposition of the aorta and pulmonary artery would result from a complete failure of their normal 180-degree torsion, as discussed in Case 1. Mitral atresia is brought by hypertrophy of the fetal endocardial cushions, which results in their fusion and complete obliteration of the atrioventricular opening. In this connection the frequent use of the word "aplasia" seems inaccurate in referring to the obliteration of the mitral valve. This word implies a failure of growth, whereas the lesion is actually a result of overgrowth, rather than undergrowth; if there were a true aplasia or failure of growth of the valve leaflets, the result would be insufficiency of the valve.

SUMMARY

1. Thirty-three cases of tricuspid atresia and twenty-eight cases of mitral atresia have previously been reported.

2. We report one additional case of tricuspid atresia associated with transposition of the aorta and atresia of the pulmonary artery, and one additional case of mitral atresia associated with complete transposition of the great vessels. Other anomalies were present in both of these cases. No cases were found in the literature in which there were these same combinations of defects.

3. The clinical and embryologic aspects of each of these lesions are discussed.

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The illness for which the patient first entered a hospital began in 1917, when he developed a left inguinal hernia. He wore a truss until 1934, when the hernia became incarcerated and increased in size. He entered the Barnes Hospital June 2, 1938, for repair of the hernia. At this time the only significant abnormalities were obesity, dental caries, and a large, indirect, left inguinal hernia. The hernia was repaired and the patient made an uneventful recovery.

He remained well until the fall of 1939, when he noticed a small mass in the right inguinal region. This disappeared when the patient lay down, but reappeared at intervals when he strained or coughed. At noon on Jan. 29, 1942, he had a sudden, severe pain in the right groin, accompanied by the appearance of a large mass in the right inguinal region which extended down into the scrotum. The mass could not be reduced, and the patient entered the Barnes Hospital that same day for immediate operation. At this time the general physical signs were the same as on the first admission, except that a soft blowing systolic murmur was now heard over the precordium; this murmur was heard best at the apex and was transmitted into the axilla. The blood pressure was 170/76. The hernia was repaired, and the patient was discharged from the hospital Feb. 13, 1942. On returning home he found that he weighed 180 pounds, which was 20 pounds less than his usual weight.

The patient felt well until early in April, 1942, when his right hand began to swell and a lump appeared on the dorsal aspect of the hand. At the same time he noticed red spots over this hand. He consulted a physician who diagnosed the lesion as a bruise, although the patient denied any trauma. The swelling and eruption gradually subsided spontaneously. Shortly after this he noticed increasing fatigability and developed a nonproductive cough. Toward the end of April he became aware of a heavy feeling in the left upper quadrant of the abdomen and a dry, burning sensation in his throat. He continued to lose weight, and, on his third admission to the Barnes Hospital, June 1, 1942, he weighed 171 pounds.

Upon admission to the hospital the temperature was 37° C., the pulse rate, 88, the respiratory rate, 20, and the blood pressure, 140/60. He did not appear ill. The skin was clear except for several red, elevated plaques varying in size on both hands. There was bilateral axillary and inguinal lymphadenopathy; the nodes in the axilla were 1 to 2 cm. in diameter, and were firm but not tender. The epitrochlear and cervical lymph nodes were not enlarged. It was noted again that the teeth were worn and carious, and that the pharynx was reddened. The lungs were normal. The heart was not enlarged to percussion. A faint systolic murmur was heard at the base, and a definite, blowing diastolic murmur was heard along the left sternal border and was transmitted down to the apex. The rhythm was regular. The liver and spleen were felt 4 cm. below the costal margins on deep inspiration. Bilateral herniorrhaphy scars were present. The prostate was moderately enlarged, smooth, and not tender.

At this time the erythrocyte count was 3,340,000 per cubic millimeter, the hemoglobin, 10.4 Gm. per 100 c.c., and the leucocyte count, 5,300 per cubic millimeter. The platelet count was 470,000 per cubic millimeter, and 2 per cent of the erythrocytes were reticulocytes. The Schilling differential leucocyte count showed 1 per cent basophiles, 12 per cent "stab" forms, 43 per cent polymorphonuclear neutrophiles, 33 per cent lymphocytes, and 13 per cent monocytes. A sternal bone marrow aspiration was performed and the marrow was normally cellular.

VEGETATIVE ENDOCARDITIS CAUSED BY HIGHER BACTERIA AND FUNGI

Review of Previous Cases and Report of Two Cases With Autopsies

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In medical literature there are comparatively few reports incriminating higher bacteria, yeasts, or fungi as the causal agents of vegetative endocarditis. Even more rare are the instances in which clinical diagnoses have been confirmed at autopsy. Because of the rare occurrence of such organisms in vegetative endocarditis, it is believed that a report of two additional cases will be of interest.* The causal agent was not detected in either case until post-mortem studies were completed. In the first case *Actinomyces graminis* was cultured from the heart's blood and from the vegetations on the mitral and aortic valves, and the organism was identified in histologic sections. *Histoplasma capsulatum* was identified in histologic sections from the second case, but was not obtained in cultures.

CASE REPORTS

Case 1.—F. T., a white married man, 55 years of age, entered the Barnes Hospital for the first time on June 2, 1938. His chief complaint at this time was of a large mass in the left inguinal region extending down into the scrotum; this had been present for twenty-one years.

There was no family history of hereditary disorders. The patient stated that his health had always been excellent. He had measles as a child and typhoid fever at the age of 19 years. There was no history of rheumatic fever. He denied ever having had a penile lesion or a skin eruption.

The patient's teeth had been in poor condition for many years. He had an occasional attack of abdominal pain after meals, and he thought that milk and milk products initiated this pain. His weight had been constant at 205 pounds for the preceding five years.

Born in Russia, the patient emigrated to Texas at the age of 30 years, and five years later moved to Illinois, where he remained the rest of his life. He married at the age of 37 years, and two years later a daughter was born. The patient operated a secondhand furniture business both in Russia and in this country, and for the preceding twenty-five years he had enjoyed a comfortable economic status. His diet was good and he did not use alcohol or tobacco.

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Received for publication March 28, 1944.

*These cases were discussed in clinicopathologic conferences at the Barnes Hospital, Cases 18 and 23, J. Missouri M. A. 40: 176, 251, 1943.

was markedly cyanotic; the skin was pale, moist, and warm. There were no petechiae or other eruptions. The pupils were small. The eye grounds were normal except for pulsating arterioles. The neck was not stiff. The neck veins were distended and the arterial pulsations were prominent. There were coarse râles and expiratory rhonchi throughout the lungs. The left border of cardiac dullness was 12 cm. to the left of the midsternal line in the fifth intercostal space. The apical impulse was not palpable, and no thrills were felt. The cardiac sounds were obscured by the pulmonary rhonchi, and no murmur could be heard. The radial pulse was of the Corrigan type. The liver and spleen were felt 4 cm. below the costal margins. The left arm and leg were flaccid. The tendon reflexes were bilaterally hyperactive, and were more active on the left. The abdominal and cremasteric reflexes were absent. Hoffmann and Babinski reflexes were present bilaterally. There was sustained ankle clonus on the right.

The erythrocyte count was now 1,750,000 per cubic millimeter, the hemoglobin, 5.8 Gm. per 100 c.c., and the leucocyte count, 17,200 per cubic millimeters. The Schilling differential count showed 10 per cent "stab" forms, 80 per cent polymorphonuclear neutrophiles, 6 per cent lymphocytes, and 4 per cent monocytes. The urine contained 1 plus albumin, and, on microscopic examination, 1 or 2 erythrocytes and 3 or 4 casts were seen per high-power field. The Kahn reaction of the blood was negative. The blood nonprotein nitrogen was 95 mg., and the blood sugar, 138 mg., per 100 cubic centimeters. The carbon dioxide combining power of the blood was 39 volumes per 100 cubic centimeters. The icterus index was 3. On blood culture *Staphylococcus albus* was isolated, but was thought to be a contaminant. The venous pressure was 210 mm. of water.

Shortly after admission a phlebotomy was performed, and 400 c.c. of blood were withdrawn. Oxygen was administered by face mask. Aminophyllin was given intravenously and digitalis intramuscularly. After this the cyanosis diminished, the breathing was less labored, and fewer râles were heard. At this time it was noted that both arms and both legs were completely flaccid. Lumbar puncture was performed, and grossly bloody fluid was obtained at an initial pressure of 300 mm. of water.

Eight hours after admission the pulse was considerably weaker; because of this and the fact that it was now known that there was considerable nitrogen retention, the blood previously withdrawn was given intravenously, together with 500 c.c. of 5 per cent glucose solution.

During the forty-eight hours the patient was in the hospital his temperature ranged between 38 and 39° C. until a few hours before death, when it reached 40° C. The pulse rate ranged between 110 and 140 per minute, and the respirations between 40 and 52 per minute. On the second day in the hospital the urine was found to contain many erythrocytes. That evening pulmonary edema returned, the respirations became more labored and rapid, and the patient died forty-eight hours after admission.

Washington University Autopsy No. 10297 (performed by Dr. W. M. Anderson).—The surface of the body was normal except for the presence of numerous petechiae in the antecubital fossae, and the healed scars of a bilateral herniorrhaphy. All lobes of the lungs were firm, poorly aerated, and deep red in color. The spleen was large, and the pulp was red and diffluent. At the upper pole there was a decolorized infarct.

The differential count on the bone marrow was within normal limits. The urine had a specific gravity of 1.016, the albumin content was 1 plus, there was no sugar, and microscopic examination revealed only a rare leucocyte and an occasional granular cast. The Kahn reaction of the blood was negative. The stool was brown and the guaiac test was negative. The blood nonprotein nitrogen was 28 mg. per 100 cubic centimeters. The icterus index was 13. The total plasma protein value was 8.2 Gm. per 100 c.c., of which 3 Gm. represented albumin, and 5.2 Gm. represented globulin. An hippuric acid liver function test was performed, and the ratio of excreted to ingested sodium benzoate was 87 per cent. Spinal puncture revealed a clear fluid which was under a pressure of 150 mm. of water. Three lymphocytes were present per cubic millimeter of spinal fluid. The protein content was 32 mg. per 100 cubic centimeters. The Wassermann reaction was negative, but the colloidal gold curve was 2555540000.

An electrocardiogram showed left axis deviation, but was otherwise normal. A roentgenogram of the chest revealed that the cardiac silhouette and aorta were within normal limits; the hilar shadows were prominent and the lungs were normal. Anteroposterior and lateral roentgenograms of the cervical spine showed moderate hypertrophic changes about the margins of the bodies of the cervical vertebrae. A special, thick barium meal showed no abnormalities in the esophagus, stomach, or duodenum.

During the eight days the patient was in the hospital his rectal temperature ranged between 37 and 37.7° C. His general condition remained unchanged. A dermatologic consultant felt that the eruption on the hands and wrists was the iris type of erythema multiforme. An otolaryngologic consultant found nothing unusual in the nose or throat. The patient was discharged with a diagnosis of aortic insufficiency and splenomegaly, cause unknown.

The patient felt fairly well for a month after his third discharge from the hospital, and gained 10 pounds in weight. However, the heavy sensation in the left upper quadrant, the nonproductive cough, and fatigability persisted. He noticed some shortness of breath on exertion, and his ankles swelled toward the end of the day. In September he began to lose weight progressively, and fatigability increased. About this time he complained of headaches every day or two, often accompanied by dizziness. In December, his cough increased in severity until it was almost constant, and was productive of a copious amount of frothy white sputum which occasionally contained black material. Early in January, 1943, he had several mild nosebleeds. At this time the heart was markedly enlarged, and a very loud diastolic murmur was heard over the entire precordium, loudest along the left sternal border. About Jan. 10, 1943, he became somewhat restless, and his wife noted that from that time on he seemed disinterested in his surroundings, but there was no mental confusion or impairment of memory. During the night of January 16 his wife heard a noise in the bathroom and found the patient lying on the floor. He was mumbling incoherently. His breathing was noisy and he was unable to raise himself from the floor. He was taken immediately to the hospital. On subsequent questioning, the patient's wife vaguely recalled that he had been a little clumsy and had limped occasionally at intervals for a month or so.

On this, his last admission, the temperature was 37° C., the pulse rate, 140, the respiratory rate, 44, and the blood pressure, 170/10. The patient was comatose and was breathing rapidly and stertorously. He

blood in the Kolmer tube and placed in a refrigerator for later studies. Cultures were incubated aerobically and anaerobically at 37° C., and observed daily for ten days. On the aerobic blood agar plate growth was first observed on the fourth day, but on subsequent transfers colonies were visible within thirty-six to forty-eight hours. Subcultures from the broth revealed growth of the same organism. Small particles of vegetations were dipped in 95 per cent ethyl alcohol and then washed in sterile physiologic salt solution. Sterile sand was added, and the vegetations were ground in a sterile mortar. The suspension thus obtained was streaked on blood agar and inoculated into tryptose-phosphate broth and incubated as already described. Colonies obtained in the aerobic plates and broth were identical with those cultured from the heart's blood. After further study the characteristics listed below were ascertained, and the organism was identified as *Actinomyces graminis* (Bostroem[1]). The patient's serum agglutinated the organism in dilutions up to 1:32, and serum from two healthy, apparently normal persons failed to cause agglutination.

1. Colonies on blood agar, forty-eight to seventy-two hours, 37° C.: round, convex, finely granular, gray-white in color, 3 to 5 mm. in diameter. Later growth was dry, umbonate, orange-brown. Tough and slightly adherent to the agar. On the sixth or seventh day colony had almost cottonlike, gray-white surface.

2. Growth in broth: ropy sediment with slight ring growth; sediment difficult to suspend by shaking.

3. Morphology of organisms (forty-eight to seventy-two hours, 37° C., blood agar): long filaments 0.6 to 0.8 μ wide, numerous long and short rods, coccoid bodies (Fig. 3). Filaments straight, wavy, and in loose groups. Conidia round or slightly elongated. Occasional branching forms. Slight tendency to formation of mycelium. No definite ray forms observed. Nonmotile. Younger growths gram positive, later becoming gram negative. Not acid-fast.

4. Physiologic reactions. Aerobic: grew poorly under reduced oxygen tension. No growth anaerobically. Would grow at room temperature. Litmus milk, peptonized in six to seven days. Gelatin, liquefied in twenty to twenty-five days. Methylene blue reduction, negative. Hydrogen sulfide production, negative. Action on sugar media: dextrose, lactose, sucrose, mannite not fermented; slight acid production in maltose.

5. Pathogenicity for animals: Intraperitoneal injection of 0.5 c.c. of broth culture produced peritonitis in guinea pigs and mice in forty-eight to seventy-two hours. Subcutaneous injections in mice and guinea pigs produced no illness or lesions. Intravenous inoculation of large doses into rabbits produced bacteremia and death in four to five days; small doses (0.2 to 0.3 c.c. of broth culture) caused no illness or lesions in animals autopsied after eight weeks of observation.

Actinomyces graminis is one of the rarer forms of this genus, but was described as a causal agent of human actinomycosis in 1891,[1] and on a few occasions since then. This is the first reported instance in which it caused vegetative endocarditis.

CASE 2.—M. G., a white man, 54 years of age, was admitted to the Barnes Hospital May 5, 1938. His complaints were of chills and fever, headaches, weight loss, and increasing weakness for five months.

The family history was irrelevant. The patient was born in Hungary. At the age of 14 years he became a baker and followed this occupation throughout the remainder of his life. He had been married twice and

The liver was large and the lobular markings were prominent. The kidneys were enlarged, each weighing 220 grams. The surfaces were finely granular, and numerous bright red petechiae studded the cortices. The brain was slightly enlarged. In the right centrum ovale there was a blood-filled cavity which measured 5 cm. in diameter. This area of hemorrhage also involved the anterior part of the thalamus and the posterior portion of the caudate nucleus. Some destruction of the anterior part of the septum pellucidum was also present. The heart was large, and weighed 550 grams. The mitral and aortic valves were moderately thickened. On both valves there were numerous, firm, gray-white vegetations covering an area 2 by 3 cm. on the mitral valve and measuring up to 1 cm. in diameter on the aortic valve. The vegetations were largest near the free margins of the cusps of the aortic valve.

Microscopic Examination.—The aortic valve was thickened and vascularized. The vegetation was composed of a large amount of fibrin, infiltrated with polymorphonuclear leucocytes. Large and small colonies of bacteria were present. These formed dense masses, so that only a few organisms could be examined in detail (Figs. 1 and 2). They were stained variably by the Gram stain. The organisms were pleomorphic; most of them were coccoid in character, but many bacillary and filamentous forms were present. A moderate amount of granulation tissue was invading the vegetation, suggesting a subacute infection. The vegetation on the mitral valve had the same histologic appearance.

The kidneys showed the changes of chronic pyelonephritis and arteriolar nephrosclerosis. In addition, there was typical, focal, embolic glomerulonephritis in different stages of healing. Spheroidal bodies of various sizes, which were regarded as forms of Actinomyces, were present in recent lesions of this sort.

The alveoli and bronchioles of the lungs were filled with an exudate of polymorphonuclear leucocytes, large numbers of erythrocytes, and a small amount of fibrin. Many spherical, rod-shaped, and short filamentous forms of Actinomyces were present in the exudate.

In the spleen, the centers of the malpighian bodies were necrotic, and appeared as irregular masses of eosinophilic material. The endothelial cells lining the sinusoids were large and prominent. In large foci the sinusoids contained many plasma cells. Large numbers of macrophages containing hemosiderin were scattered throughout the spleen.

The wall of the cavity in the brain contained several small arteries, the walls of which showed acute inflammatory reactions. Polymorphonuclear leucocytes were present in and around the walls of these vessels.

The other organs of the body showed no relevant pathologic change. The significant pathologic changes were:

Subacute bacterial endocarditis of the aortic and mitral valves (*Actinomyces graminis*).
Focal, embolic glomerulonephritis.
Acute arteritis of small cerebral arteries.
Hemorrhage into the right cerebral hemisphere.
Bronchopneumonia of all lobes of the lungs.

Bacteriologic Studies.—At autopsy 10 c.c. of blood were removed from the right atrium and added to a tube containing 30 c.c. of tryptose-phosphate broth (Difco). In addition, 5 c.c. of blood were placed in a sterile Kolmer tube, and a loopful of blood was streaked on two blood agar plates (5 per cent rabbit's blood). Para-amino benzoic acid (5 mg. per 100 c.c.) was added to the media. Serum was collected from the

had two daughters by his first wife, whom he later divorced. During the first World War he traveled with army troops as a cook until he became a victim of "shell shock." Thereafter, he had amnesia regarding his army experiences. In 1922 he came to St. Louis, where he lived the remainder of his life.

Other than "shell shock," the only significant illness occurred at the age of 40 years, when the patient suddenly fainted and a short time later passed a copious, black stool. There were no other gastrointestinal symptoms and he continued work without interruption or recurrence of such attacks. There was no history of rheumatic fever, a penile sore, or a skin eruption of any sort.

The systemic review revealed that he had had frequent headaches for three or four years previous to admission to the hospital. His wife stated that frequently during these years he had shaking movements of the lower extremities during sleep.

The present illness began five months before admission to the hospital, when the patient became weak and drowsy. This was followed by the onset of chills, fever, and profuse sweating. His physician made a diagnosis of "grippe," and the patient remained in bed for a week. He then resumed work, but his symptoms returned and progressed. A few weeks later the patient was told by another physician that he had undulant fever. Blood tests were made, and he was told that he had syphilis as well as undulant fever. The patient was treated with tablets by mouth and almost daily intramuscular injections, but general malaise, weakness, and profuse sweating became more pronounced. He continued to have chills and fever and gradually became somewhat drowsy. Loss of appetite was progressive, and his weight decreased from 153 to 123 pounds in five months.

Upon admission, the temperature was 38.2° C., the pulse rate, 90, the respiratory rate, 20, and the blood pressure, 120/80. The patient appeared chronically ill and had obviously lost weight. He was drowsy, but conscious and well oriented. The skin was moist. The epitrochlear lymph nodes were moderately enlarged; no other nodes were palpable. The pupils were contracted. They reacted in accommodation but not to light. The mouth was edentulous. The tonsils were large, with caseous material in the crypts. There was a fine fibrillary tremor of the tongue. Chest expansion was poor, and the diaphragm moved but little to percussion. The heart was moderately enlarged. The rhythm was regular, and the sounds were of good quality. At the aortic area the second sound was loud, and there was a systolic murmur. The lungs were normal except for a few cracking basal râles which did not disappear on coughing. The abdomen was flat and relaxed. The liver was felt at the costal margin; the spleen and kidneys were not palpable. The tendon reflexes were hyperactive except for the left ankle jerk, which was barely obtainable. Sustained ankle clonus was present on the right. In the Romberg position there was slight swaying.

The hemoglobin was 82 per cent; the erythrocytes numbered 4,270,000, and the leucocytes, 4,000 per cubic millimeter. The Schilling differential count showed 14 per cent "stab" forms, 47 per cent polymorphonuclear leucocytes, 35 per cent lymphocytes, and 4 per cent monocytes. On another occasion 10 per cent of the leucocytes were monocytes. Urinalysis was negative except for 1 plus albumin. The blood Kahn and Wassermann reactions were strongly positive. Serum agglutination tests with typhoid and Brucella organisms were negative. Three routine blood cultures showed no growth. The blood sugar level was 86 mg., the urea nitrogen, 17 mg., the calcium, 8.7 mg., the phosphorus, 3.3 mg., and the

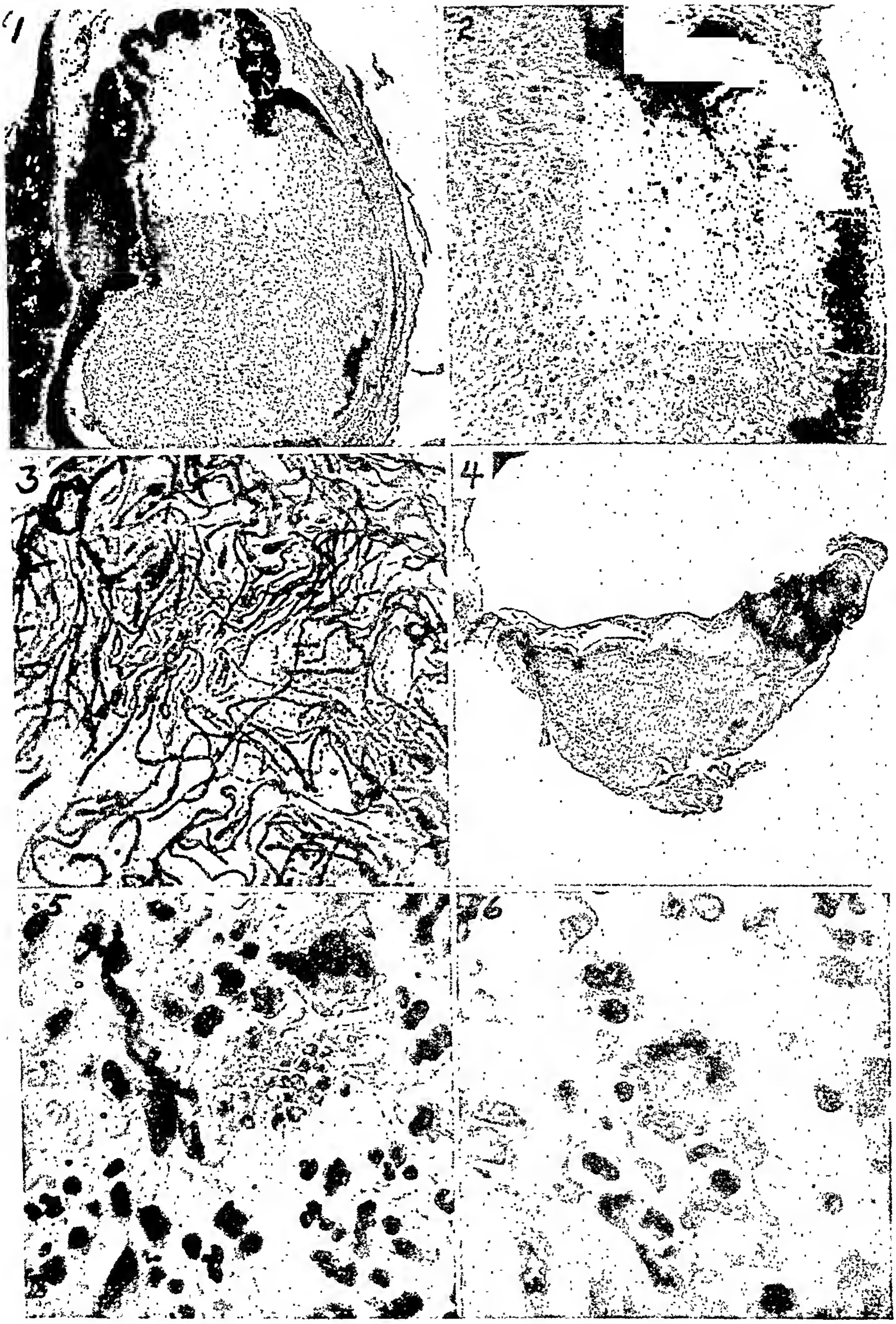

Fig. 1.—Section of vegetation (Case 1) from the aortic valve, showing dense masses of organisms surrounding granulation tissue (×30).

Fig. 2.—Section of vegetation shown in Fig. 1 under higher power (×470).

Fig. 3.—Photomicrograph of preparation (Gram stain) from forty-eight-hour culture of *Actinomyces graminis* on blood agar. Numerous filamentous, bacillary, and coccoid forms are present. Occasional branching is observed (×870).

Fig. 4.—Section of aortic valve and vegetation (Case 2), showing marked thickening of the valve (×7.5).

Fig. 5.—Higher power view of granulomatous lesion in the aortic valve (Case 2), showing several cells of *Histoplasma capsulatum* in a macrophage (×1,100).

Fig. 6—Granulomatous focus in the kidney (Case 2), showing a giant cell containing yeastlike cells, *Histoplasma capsulatum* (×1,100).

the surface, where the vegetation was, there was a large amount of granulation tissue. The vegetation consisted of a moderate amount of fibrin, with a cellular reaction composed of polymorphonuclear leucocytes, lymphocytes, and plasma cells (Fig. 4). No bacteria were visible in the vegetation. In the valve beneath the vegetation, there were areas of necrosis of various sizes, with necrotic cellular debris in the centers, and peripheral zones of lymphocytes, plasma cells, and macrophages. In some of these foci, macrophages were seen to contain minute spherical bodies composed of a basophilic central portion, with a clear, nonstaining peripheral halo (Fig. 5). These organisms had the morphologic characteristics of *Histoplasma capsulatum*. The kidneys, liver, spleen, pancreas, and brain presented numerous granulomatous areas of necrosis. These consisted of a central area of necrosis, surrounded by large epithelioid cells, one or more giant cells of the Langhans type, and a peripheral zone of lymphocytes and large numbers of plasma cells. These foci were scattered throughout the organs mentioned, with no specific predilection as to site. The lesions were most abundant in the kidneys and spleen, and were less frequent in the liver, pancreas, and brain. In some granulomatous foci, organisms identical with those in the valve were present (Fig. 6). In the kidneys, occasional glomeruli were partially destroyed by thrombi which involved parts of the capillary loops.

Summary of the significant pathologic changes:

Histoplasmosis involving the cusps of the aortic valve, kidneys, spleen, liver, and brain.
Thrombi in small arteries and veins of spleen, kidney, and intestinal wall.
Infarcts of the spleen.
Bronchopneumonia of the lower lobes of the lungs.
Syphilitic aortitis and aortic valvulitis.

REVIEW OF LITERATURE AND DISCUSSION

In recent years an increasing number of reports have appeared concerning patients with vegetative endocarditis caused by higher bacteria, yeasts, or fungi. For example, the recording of several cases of Candida (Monilia) endocarditis[2-6] in three years has aroused renewed interest in a mycotic infection which is known to be frequent and widespread. Furthermore, there are several reports which describe Actinomyces,[8-10] Erysipelothrix,[11, 12, 23, 24] and Leptothrix[13] as the causal agents of vegetative endocarditis, and recently a case caused by *Histoplasma capsulatum* was reported.[14]

In a statistical survey of actinomycosis in the United States, Sanford and Voelker[16] reviewed 670 cases, but found no instance in which the heart was involved. However, such involvement was observed by workers[17-20] in other countries, and later by Kasper and Pinner[21] in this country. In each of these instances, however, lesions were found in the myocardium but not on the valves. Dean[7] and Harbitz and Gröndahl[19] described two cases in which endocardial lesions were present as a result of direct extension from a focus in the myocardium.

Alestra and Girolami[8] were the first to report a case of vegetative endocarditis in which Actinomyces (Nocardia, species not ascertained) were

phosphatase, 4 Bodansky units per 100 cubic centimeters. The total plasma protein value was 7.8 Gm. per 100 c.c., of which 2.6 Gm. was albumin, and 5.2 Gm., globulin. Both the Takata-Ara and formol-gel tests were strongly positive. The stool was guaiac positive. The spinal fluid was clear; it contained 3 cells per c.mm. and 88 mg. of protein per 100 cubic centimeters. The spinal fluid Wassermann reaction was positive, and the colloidal gold curve was 5555555553. Brucellin and tuberculin skin tests were negative. The sternal bone marrow contained 6.5 per cent plasma cells, but was otherwise normal.

An electrocardiogram showed only left axis deviation. Roentgenographic examination of the chest revealed cardiac enlargement, widening of the superior vena cava, and infiltration of the right lower lung field. Lipiodol bronchograms were made, and there was no evidence of bronchiectasis. A posteroanterior roentgenkymogram of the heart indicated that the movements of the left ventricle were small in amplitude. Bronchoscopic examination revealed general hyperemia of the bronchial mucosa.

During the eleven weeks the patient was in the hospital he ran a continuous, high, spiking fever. He was given quinine for two days, and then atabrine for five days without effect on the fever or symptoms. He received 1.2 Gm. of sulfanilamide four times daily for four days; several weeks later this drug was administered again for eight days and there was no effect in either instance. The patient continued to have chills occasionally and was drowsy most of the time. During the fifth week in the hospital, basal râles, enlargement of the liver, and edema of the ankles were noted. He was digitalized without much improvement. During the few weeks before death he became more and more drowsy, and the blood urea nitrogen rose steadily to a level of 117 mg. per 100 cubic centimeters. Albumin, casts, and erythrocytes were found in the urine in increasing amounts. There was a persistent leucopenia; the leucocyte count ranged between 3,500 and 7,100 per cubic millimeter, and the differential count at all times showed a considerable increase in the percentage of young myeloid forms. The patient died in coma on the seventy-seventh hospital day.

Washington University Autopsy No. 7605 (performed by Dr. A. Mueller).—The body was that of a well-developed, poorly nourished white man. The external appearance was normal. The serous cavities contained no abnormal amount of fluid. The heart was normal externally. The aortic valve was thickened throughout, and one cusp was covered by a friable vegetation which involved both the ventricular and aortic surfaces. This vegetation measured about 1 cm. in diameter. A small, similar vegetation was present on another cusp of the aortic valve. The other valves were normal. The ascending aorta was widened and wrinkled. Section of its wall revealed degeneration of the media in many areas. The lungs were moist, and frothy fluid was easily expressed from the cut surface. There were fine, fragile adhesions in the right pleural cavity. No areas of consolidation were present in the lungs. The spleen was large, and weighed 390 grams. It contained numerous infarcts of varying ages. The kidneys were large, and weighed 240 and 230 grams, respectively. The surfaces were smooth, and prominent vessels were observed. The cortex and medulla of each were somewhat thickened. A vessel containing a thrombus was present near the pelvis of the left kidney. The brain was softer than usual, but was otherwise normal. No other organs showed any relevant pathologic changes.

Microscopic Examination.—The aortic valve contained a marked increase in fibrous tissue. There were many areas of calcification. Near

and in most of them the organism was cultured from the blood during life and its causal relation confirmed by post-mortem mycologic and histologic studies. However, in one case[2] ante-mortem blood cultures yielded no growth, and, although the yeastlike organisms were observed in microscopic sections, post-mortem mycologic studies were not completed. Consequently, an accurate identification of the causal agent was not made. In the cases observed at autopsy the vegetations were engrafted upon already damaged valves, most frequently on the aortic.

The clinical diagnosis of vegetative endocarditis is not particularly difficult, even though the causal agent may not be one of the more common, and frequently recognized, true bacteria. A review of cases already reported reveals that there have been ten instances, confirmed at autopsy, in which a higher bacterium, a yeast, or a fungus was the causal agent. In all ten of these the diagnosis was based clinically on important signs and symptoms characteristic of vegetative endocarditis. Positive blood cultures were obtained in eight cases during life. The two remaining, in which no growth was obtained, were diagnosed after death as vegetative endocarditis caused by a yeast and by *Histoplasma capsulatum*.

Several factors influence the degree of success with which conclusive, positive cultures are obtained from blood and tissues. Of course, it is necessary to provide satisfactory nutritional substances and environmental conditions for the growth of the microorganisms. This frequently involves special media, containing additional nutritive substances, and modified atmospheric conditions, such as reduced oxygen tension and strictly anaerobic containers. However, the factor which is probably overlooked most frequently is the period of incubation. Several microorganisms, for example, certain higher bacteria, yeasts, and fungi, although they can develop on ordinary blood agar or carbohydrate media, do not "grow out" as rapidly as the more commonly encountered, true bacteria. Specifically, one may mention *Histoplasma capsulatum* as an example. This organism will develop on blood agar or plain carbohydrate media, but various reports indicate that an incubation period of twelve or more days may be necessary. In other instances, this organism has been observed on blood agar plates as early as the fourth to sixth day of incubation. Another example is the Actinomyces, which frequently require four or five days to produce visible growth. Consequently, when a clinical diagnosis of bacterial endocarditis is made, and blood cultures fail to show the usual organisms encountered in this condition, attention should be directed to the possibility that another causal agent is present. The routine technique must be modified sufficiently for successful culture and detection of less common microorganisms.

The natural habitat of many higher bacteria, yeasts, and fungi is widespread. Frequently, laboratory workers are not familiar with pertinent facts about such microorganisms, or, in other instances, may recognize

cultured from the blood during life, and confirmed their diagnosis by demonstrating the organisms in histologic sections and in cultures from the vegetation after death. They also studied another case of endocarditis in which Actinomyces (Nocardia, species not ascertained) were cultured from the blood during life. This patient, however, apparently recovered under therapy with an iodine compound ("Septojod"). The second authentic case of actinomycotic endocarditis was that reported by Uhr,[10] in which the causal agent, *Actinomyces bovis*, was isolated from the blood during life and its causal relation confirmed at autopsy. No other proved examples of actinomycotic endocarditis were found in the literature. Freeman[9] reported a case, diagnosed clinically as bacterial endocarditis, in which "an unusual bacillus" was isolated from the blood on three successive occasions. The organism was tentatively placed in the order Actinomycetales, but was not definitely identified. The patient died at home after a typical clinical course of subacute bacterial endocarditis, and no autopsy was performed.

Russell and Lamb[11] and Klauder, Kramer, and Nicholas[12] reported endocarditis in two cases of septicemia caused by *Erysipelothrix rhusopathiae;* this was confirmed by histologic and post-mortem bacteriologic studies. This organism is related, at least morphologically and physiologically, to Actinomyces. Three additional instances of this disease are reported in other papers, but, in two,[23] there was no bacteriologic confirmation of the histologic diagnosis, and, in the other,[24] no autopsy was performed.

Another interesting example of vegetative endocarditis caused by higher bacteria is that reported by Jervell[13] in a young man who died eight weeks after the onset of symptoms typical of vegetative endocarditis. Cultures of the blood during life and after death revealed the presence of Leptothrix, which was also cultured from the vegetations.

Histoplasmosis, a subacute or chronic, highly fatal, infectious disease caused by an intracellular yeastlike organism, occurs at all ages and in both sexes. Depending on the dominant clinical picture, the disease may be classified into several types, for example, generalized, pulmonary, intestinal, naso-oral, cutaneous, and joint types.[22] Although the infection was first described in 1906, and the reported cases number over fifty, Broders, Dochat, Herrell, and Vaughn[14] recently published the first paper describing vegetative endocarditis in association with a generalized infection by *Histoplasma capsulatum*. Moreover, in a paper now in preparation, Parsons[15] is citing at least two additional cases. Perhaps on re-examination of sections in various laboratories other instances will be discovered.*

During the past three years, six cases of endocarditis were described in which *Candida parakrusei* or *guillermondi* was the causal agent. All but one of these occurred in drug addicts. These patients presented signs and symptoms which led to the diagnosis of bacterial endocarditis,

*It is of interest that in the case reported in this paper the diagnosis was not made until Dr. M. G. Smith re-examined the sections at a later date.

(c) The serum proteins in the present cases were elevated, with reversal of the albumin-globulin ratio (in the other cases no data are available for comparison).

(d) In the presence of the usual signs and symptoms of vegetative endocarditis, negative blood cultures by routine procedures may suggest a less common causal agent.

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the forms but tend to consider them as contaminants. As Pasternack[5] has emphasized, cultures showing molds or yeasts are frequently discarded. Even after repeated culture, their presence often is attributed to a defect in technique. Recent reports of human infection caused by such microorganisms indicate that they may be more common as causal agents than was previously supposed.

Although the series of cases of vegetative endocarditis caused by higher bacteria, yeasts, or fungi is small, certain interesting facts are noted. There were ten cases[2, 3, 5, 6, 8, 10-14] with sufficient clinical data and autopsy studies to make comparisons with the two reported in this paper. Of the twelve cases, four were caused by Candida (Monilia), three by Actinomyces, two by *Erysipelothrix rhusopathiae,* two by *Histoplasma capsulatum,* and one by Leptothrix. Eleven of the patients were men, ten of whom were 35 years of age or over. In only two instances did the disease run a clinical course of less than two months; the average in the twelve cases was seven months. It is interesting that in the two cases of histoplasmosis there was a relative leucopenia, varying between 4,000 and 7,000, in contrast to the mild or moderate leucocytosis observed in the others. Of interest, also, is the elevation of serum proteins in both cases reported in this paper, with hyperglobulinemia as high as 5.2 Gm. per 100 cubic centimeters. In our case of histoplasmosis, this was attributed to syphilis, but it may be that the hyperglobulinemia was related to the primary infection in both instances. No serum protein determinations were recorded in the ten cases reviewed from the literature.

Autopsy studies reveal that vegetations caused by Candida (Monilia), two of the Actinomyces, the Leptothrix, and both strains of Histoplasma were engrafted upon valves showing sclerosis and calcification, chronic endocarditis, or syphilitic valvulitis. However, one strain of *Actinomyces bovis*[10] and both strains of Erysipelothrix attacked normal valves. Of the twelve cases under consideration, the aortic and mitral valves were involved in four, the aortic alone in five, the mitral alone in two, and the pulmonic in one case.

SUMMARY

1. Two cases of vegetative endocarditis are reported; in one, *Actinomyces graminis* was the cause, and, in the other, *Histoplasma capsulatum.*

2. Ten previously reported cases of vegetative endocarditis caused by higher bacteria, yeasts, or fungi [Candida (Monilia), Actinomyces, Leptothrix, Erysipelothrix and Histoplasma] are reviewed briefly and compared with the present cases.

3. From a study of twelve cases with autopsies, the following points may be of assistance in differentiating between vegetative endocarditis caused by bacteria and that caused by these higher forms:

(a) Greater incidence in men.

(b) Most patients were over 35 years of age.

moreover, greatly exceeded the incidence of hyperresponse in the school children observed by Hines.[6] Consequently, an appreciable percentage of these adult hyperreactors and/or hypertensives must have been hyporeactors as children. These considerations seemed to invalidate the view that hyperreaction is always an inherited and lifelong trait, closely correlated with a family history of hypertensive cardiovascular disease. Obviously, if this were the case, a positive history would indicate, paradoxically, a greater life expectancy, for the percentage of hyperreactors increased sharply with advancing age. Actual analysis, however, disclosed no relationship between the nature of the cold-pressor response and the family history of hypertensive disease. The results of that study, therefore, cast doubt upon the concept that hyperreaction is a precursor of sustained hypertension.

The present analysis was undertaken to explore these discordant views and to obtain additional data on normal persons. Since all previous studies of the cold-pressor response of normal persons arbitrarily accepted 145/95 as the upper limit of normal blood pressure, it seemed to us that this relatively high level may have permitted the inclusion of a variable number of hypertensive subjects with borderline pressures. Ayman[17] also expressed the view that some of the subjects studied may actually have been mild hypertensives, and advised that only cases in which there could be no doubt about normal status be selected. The follow-up studies of Hines,[12] furthermore, offered a rational method of classifying normal and abnormal pressures, and suggested to us a means of testing the validity of the theory proposed by Hines and Brown. In a survey of the blood pressure variations among clinic patients, Hines noted that the reading of 140/85 on first examination represented a critical level with respect to the possible occurrence of subsequent hypertension. Thus, the subjects whose systolic and diastolic blood pressure was originally in the upper range of normal (140 to 160 mm., systolic, and 85 to 100 mm., diastolic) manifested a high incidence of ensuing hypertension; whereas only a small number of those who originally had blood pressure levels in the lower range of normal subsequently developed the disease. According to Hines, therefore, the vasomotor response to the nervous stress of the physical examination serves as a "psychic-pressor test," and presents implications similar to those derived from the pressor effect of a standard stimulus of cold.

With these considerations in view, it was decided to adopt the critical level of 140/85 to differentiate nonhypertensive from prehypertensive subjects. It seemed possible by this means to obtain a group of "pure normals" who, if Hines' presumptions are correct, would manifest a strikingly low incidence of hyperreaction to the cold-pressor test. Accordingly, further studies of the cold-pressor response of healthy seamen were undertaken; the subjects were classified with respect to initial blood pressure readings into two groups, as follows: (1) Nonhypertensive subjects (initial blood pressure below 140/85), and (2) prehypertensive subjects (initial blood pressure 140/85 or above).

NFLUENCE OF AGE UPON BLOOD PRESSURE RESPONSE TO THE COLD-PRESSOR TEST

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SSENTIAL hypertension has been defined as a syndrome which is limited to persons with a hyperreactive vascular system.[1-14] This yperreactive state, according to Hines and Brown, can be demonstrated en in childhood among persons destined to develop the disease. In pport of this hypothesis, Hines[10] asserts that (1) hyperreaction to the ld-pressor test is found among people with normal blood pressure and similar to the reaction observed in essential hypertension; (2) patients ho were formerly hypertensive show a hyperreactive response even if eir blood pressure is normal; (3) the incidence of hyperreaction in ildren approximates the combined incidence of hyperreaction and hyertension in adults; (4) hyperreactors with normal blood pressure generally come from families in which there is a high incidence of hypernsive cardiovascular disease; and (5) hypertension has developed in veral patients whose blood pressure was once normal but who showed yperreaction to the test.

Although these contentions strongly suggest that abnormal variability f the blood pressure is a heralding sign of subsequent hypertension, the bservations of one of us (H. I. R.)[15, 16] failed to support this concept. n a study of two hundred normal seamen over the age of 40 years, it as found that the cold-pressor reaction did not remain constant roughout life, as alleged by Hines and Brown, but increased appreciably with advancing age. The augmented response, furthermore, aplied not only to hyperreactors but also to hyporeactors (persons who howed a normal response, more correctly, normal reactors), which ustifies the conclusion that vascular reactibility increases as a natural onsequence of the aging process. From this it appeared that a hypoeactor at 40 years might become a hyperreactor at 50 or 60 years of age. Such a trend was further reflected in the rising incidence of hyperreection with succeeding decades. Thus, the percentage of hyperreactors ncreased from 24.2 per cent in the 40- to 49-year group to 56.1 per cent n the 60- to 69-year group. On the other hand, if hyperreaction were n reality the prehypertensive phase of essential hypertension, the reerse thereof, namely, a falling incidence of "normal" hyperreactors, vould have been observed with advancing age. The combined incidence of hyperresponse and hypertension in the elderly subjects of the series,

From the Cardiovascular Service, U. S. Marine Hospital.
Published with the permission of the Surgeon General, United States Public Health Service.
Received for publication April 10, 1944.

TABLE II

PERCENTAGE INCIDENCE OF HYPERREACTION BY AGE AND INITIAL BLOOD PRESSURE LEVEL

AGE (YRS.)	LESS THAN 140/85 (240)	140/85 TO 160/100 (110)	160/100 AND LESS (350)
40 to 49	24.7	66.7	34.8
50 to 59	42.0	70.0	52.2
60 to 69	56.7	75.8	63.0
40 to 69	40.0	70.9	49.7

actors to the cold-pressor test. When the analysis was carried further, and the two blood pressure groups were studied independently, it was found that the rising incidence of hyperreaction was particularly marked in the nonhypertensive class, in which the increase was from 24.7 per cent in the fifth decade to 56.7 per cent in the seventh decade. In the prehypertensive group, on the other hand, the incidence of hyperreaction increased more slowly with age, rising from 66.7 per cent to 75.8 per cent in the same period. Hyperreactors comprised 70.9 per cent of the prehypertensive subjects, as compared with 40 per cent of the nonhypertensive subjects.

DISCUSSION

Abnormal variability of the blood pressure is regarded by many authors as one of the outstanding characteristics of essential hypertension. In the opinion of Hines and Brown, vascular hyperreaction in persons with normal blood pressure means either a predisposition to hypertensive disease, or previous hypertension which is temporarily latent. Other observers,[18-23] similarly, have emphasized the prognostic significance of even transient elevation of the blood pressure in subjects who generally have normal levels.

Our observations strongly suggest, however, that excessive reactibility of the blood pressure may be a physiologic occurrence in the later decades of life. This conclusion is based upon the observation that the vasopressor response to a standard cold stimulus rises appreciably with advancing age. In our series, an increase in the range of reaction was noted not only among hyperreactors, as reported by Hines and Brown, but also among hyporeactors. As would be anticipated, the incidence of hyperreaction showed a corresponding rise with age, so that hyperresponse was almost twice as frequent in the seventh decade as in the fifth. These observations suggest that age exerts an important influence upon the response of the blood pressure to a standard stimulus of cold.

The tendency for a normal reaction to become "excessive" was unrelated to the initial blood pressure level, inasmuch as the hyporeactors in both blood pressure groups showed a similar increase in response with succeeding decades. The incidence of hyperreaction increased with age in the nonhypertensive group from 24.7 per cent to 56.7 per cent, and, in the prehypertensive group, from 66.7 per cent to 75.8 per cent.

TECHNIQUE OF THE COLD-PRESSOR TEST

The procedure as outlined by Hines and Brown was followed throughout. The subjects remained recumbent in a quiet room, and blood pressure readings were taken over variable periods until a basal level was reached. The rest period was twenty to thirty minutes, and, usually, four to five readings were made. The sphygmomanometer cuff remained on the arm during the whole procedure, and, when the lowest level of blood pressure was reached, the free hand was placed in a basin of water at a temperature of 4° C. The hand was kept immersed to a level just above the wrist for sixty seconds. The blood pressure was measured at thirty and sixty seconds.

The response is recorded as the difference between the basal level and the maximum reading. Using the authors' criteria, subjects whose response exceeded 20 mm., systolic, and 15 mm., diastolic, were called hyperreactors. Those whose response did not exceed these figures were designated as hyporeactors.

RESULTS

The test was performed on three hundred fifty merchant seamen between the ages of 40 and 69 years. Data on two hundred of these subjects formed the basis of a previous report.[15] All were ambulant hospital patients who had been admitted for a variety of minor ailments unrelated to the cardiovascular system. The initial blood pressure on admission to the hospital was used to classify these patients in the manner described above. There were two hundred forty subjects in the nonhypertensive group and one hundred ten subjects in the prehypertensive group. The highest initial pressure in the study did not exceed 160/100.

In Table I the average response of the blood pressure to a standard stimulus of cold is analyzed with respect to age, initial blood pressure level, and type of response. It is seen that there was an appreciable rise with age in the average response of all subjects, whether they were hyporeactors or hyperreactors. Even when the subjects with lower levels of normal blood pressure were considered as a group, this increase in average vasoconstrictor response with advancing age was clearly evident.

Table II shows that when all subjects were considered, there was an appreciable increase in the incidence of hyperreaction with succeeding decades. The frequency rose from 34.8 per cent to 63 per cent in the age period studied. Of the entire group, 49.7 per cent were hyperre-

TABLE I

ANALYSIS OF COLD-PRESSOR RESPONSE BY AGE AND INITIAL BLOOD PRESSURE LEVEL

AGE (YRS.)	BLOOD PRESSURE 160/100 AND LESS				BLOOD PRESSURE LESS THAN 140/85			
	HYPOREACTORS		HYPERREACTORS		HYPOREACTORS		HYPERREACTORS	
	SYST.	DIAST.	SYST.	DIAST.	SYST.	DIAST.	SYST.	DIAST.
40 to 49	10.1	7.6	25.0	18.6	10.0	7.5	24.6	18.0
50 to 59	16.0	11.4	33.2	23.2	15.2	11.5	32.0	22.1
60 to 69	17.3	13.3	35.6	24.6	17.1	13.1	35.2	22.1

(prehypertensive) and that of persons with initial pressures in the lower range of normal (nonhypertensive). It was concluded that:

1. The response of the blood pressure to a standard stimulus of cold tends to increase in all subjects with advancing age.

2. The rising response appears to result from increasing irritability of the vasomotor centers, an effect of the vascular changes associated with "aging."

3. The tendency for a normal reaction to become "excessive" is reflected in the rising incidence of hyperreaction with succeeding decades.

4. There is a marked increase in the frequency of hyperreaction with advancing age among "subjects unlikely to develop hypertension," suggesting that such a response is frequently physiologic in the later decades of life.

5. Hyperreaction is more common among prehypertensive subjects than among nonhypertensive persons, but the difference in frequency between the respective groups becomes much less marked with advance of age.

6. The high incidence of hyperreaction among the nonhypertensive subjects indicates that such a response cannot be regarded as specific for potential or latent hypertension at this age.

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Hyperreaction was found in 70.9 per cent of the subjects who were likely to develop hypertension, as compared with only 40 per cent of those who were unlikely to develop it. This difference is statistically significant, and clearly indicates that hyperresponse is more common among subjects destined to develop the disease. Nevertheless, the high incidence of vascular hyperreaction among nonhypertensive subjects makes it equally apparent that no specific correlation exists between hyperresponse and subsequent hypertension. In this regard, it should be noted that the older the group considered, the less was the disparity in incidence of hyperreaction between the respective blood pressure groups. Vascular hyperreaction, therefore, appears to arise, in later life at least, from factors related to the aging process.

From these observations it would seem that there is a progressive increase in the irritability of the vasomotor mechanism with advancing age. A similar conclusion was reached by Raab[24] in his studies of the blood pressure response to the inhalation of carbon dioxide. In reporting the pressor effect at various ages, the author stated that there is "increasing irritability of the cerebro-medullary vasoconstrictor centers" with advancing years. He attributed the rising vasopressor response to a gradual diminution in cerebral blood flow, which leads to ischemia of the nerve centers controlling vascular tonicity. Others have shown, moreover, that arteriolar sclerotic changes, associated with decreased cerebral blood flow, are common features of advancing age. Consequently, Raab's observations, employing the stimulus of carbon dioxide, are supported by our own observations, using the stimulus of cold.

It appears from this evidence that cerebral vascular ischemia develops in an increasing percentage of persons with advancing age. Whether or not such central changes and their consequences are always to be regarded as pathologic is still an unanswered question. The recent experiments of Fishback and his co-workers[25] suggest that decreased cerebral blood flow may be an important factor in the etiology of hypertension. These authors were able to produce sustained elevation of blood pressure in animals by ligating arteries supplying the head. On the other hand, it would seem from our data that cerebral ischemia, as manifested by vascular hyperreaction, is found in a significantly high percentage of older persons who never develop hypertensive disease. We have noted, in fact, that hyperresponse is not uncommon even in "hypotensive" subjects (systolic pressure 110 mm., or less) in the later decades of life. It cannot be denied, therefore, that vascular hyperreaction may be physiologic in many middle-aged and elderly subjects.

SUMMARY AND CONCLUSIONS

The cold-presser reaction of three hundred fifty male subjects over the age of 40 years was measured. A comparison was made between the response of persons with initial pressures in the upper range of normal

Clinical Reports

BUNDLE BRANCH BLOCK, WITH SPONTANEOUS REMISSION AFTER FOUR YEARS

Report of a Case

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THERE have of late been increasing numbers of reports of transient, complete, bundle branch block, but all writers agree that, once established, the block will remain as a permanent feature. A careful search of the literature failed to reveal any case in which bundle branch block persisted over a period of years and disappeared spontaneously. In a personal communication, Dr. Paul White, of Boston, stated, "I have never seen or heard of a patient whose electrocardiogram returned to normal after years of constant bundle branch block." A similar communication from Dr. H. M. Marvin, of New Haven, Conn., confirmed this opinion, and both, after reviewing the electrocardiograms, suggested the desirability of reporting this case.

CASE REPORT

R. D., aged 56 years, a white man, first presented himself for examination on Sept. 13, 1938. Two years previously, while shoveling snow, the patient collapsed. He recalled no accompanying pain. Two weeks later he had another attack, this time accompanied by a moderate amount of precordial pressure which lasted about twenty-four hours. The patient was apparently told that he had "heart disease," and was advised "to avoid excitement and take things easy." Retirement from active work had been advised. His only complaint at the time of his first visit was of moderate fatigability.

Physical examination revealed a well-nourished and well-developed man who weighed 194 pounds. The pulse was regular and the rate was 86. There was moderate retinal sclerosis. The chest wall was rather thick and the thorax was emphysematous. The heart sounds were somewhat distant, but well heard. There were no murmurs. The blood pressure was 116/80. The blood Wassermann reaction and urinalysis were negative. Fluoroscopic examination showed moderate enlargement of the left ventricle and some elongation of the thoracic aorta. An electrocardiogram on Sept. 13, 1938 (Fig. 1), showed left bundle branch block. The P-R interval was 0.16 to 0.18 second. T-wave inversion was present in Lead I. The QRS interval was 0.15 second.

Received for publication Aug. 13, 1943.
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that bundle branch block, once established in cases of organic heart disease, remains throughout life. Transient, complete, bundle branch block has been rather infrequently reported. In the series of cases reported by Kurtz,[1] bundle branch block had a duration of a few moments to ten months, but he concludes that, once established, the block persists for the remainder of the patient's life. Master, Dack,

I

II

III

IVF

IVR

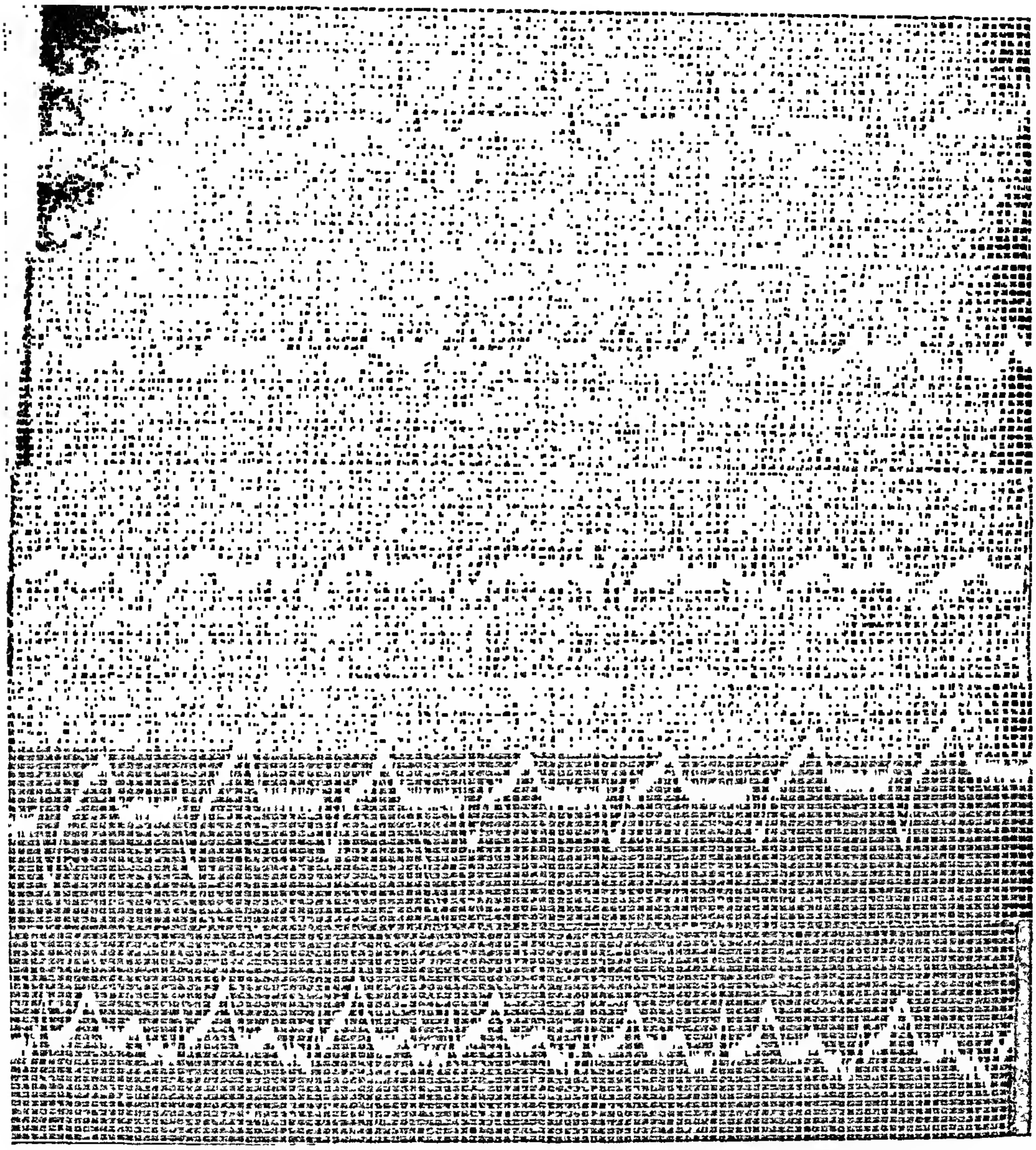

Fig. 2.—As in Fig. 1. Taken Feb. 6, 1940.

and Jaffe[2] wrote: "The conduction defect persisted in 23 patients until death. . . . In 27 patients who survived, the conduction defect was still present in records taken several months to two years later." In a single case reported by Bishop,[3] the transient, recurrent, bundle branch block lasted about six months. It later became permanent.

The patient left New Britain and was not seen again until Feb. 6, 1940. At this time there was little change in the physical signs, and there were no symptoms. An electrocardiogram (Fig. 2) showed left bundle branch block exactly as before.

The patient, unfortunately, was not seen again until Oct. 3, 1942. At no time had he had any symptoms. An electrocardiogram which was taken

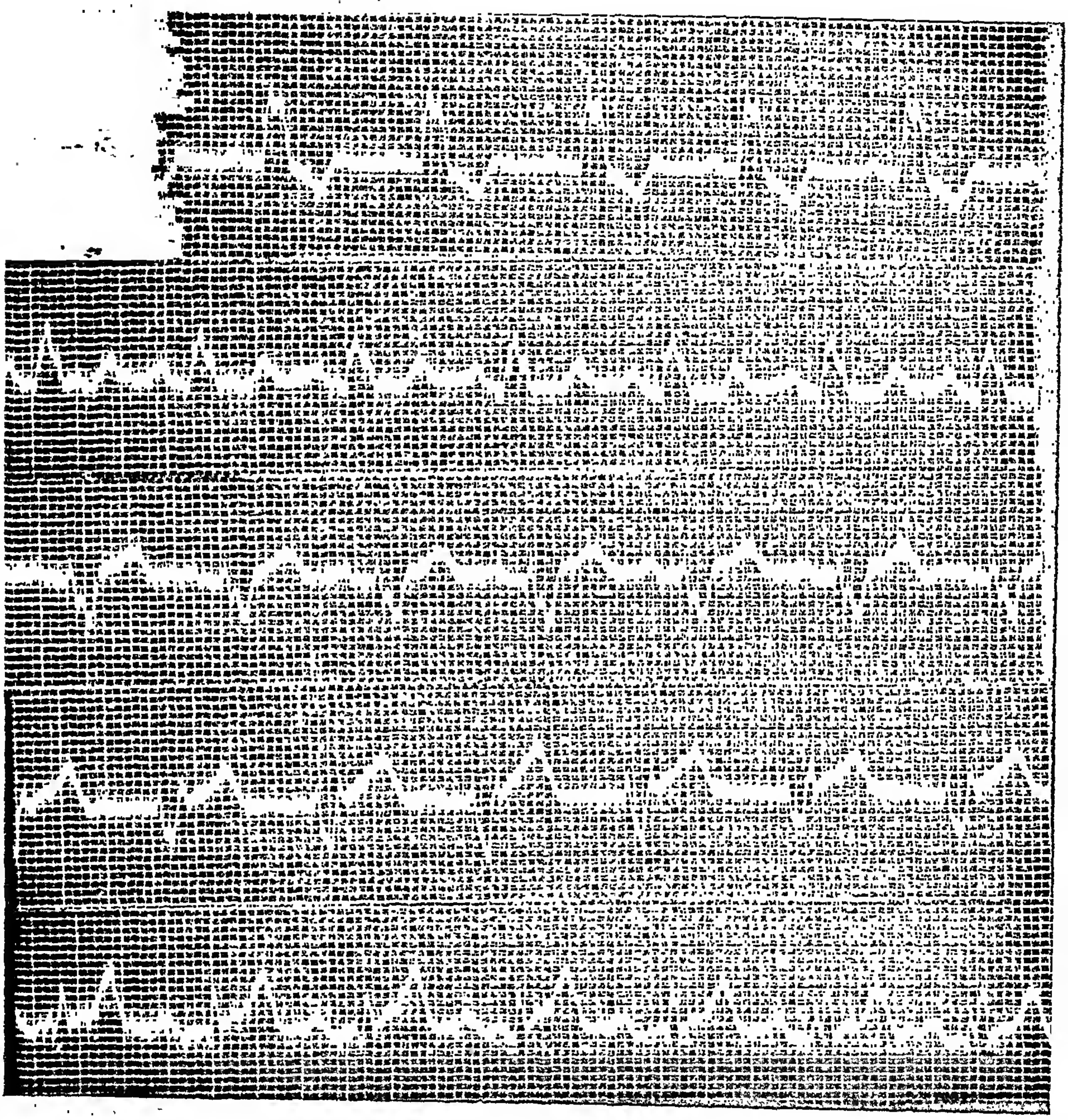

Fig. 1.—Taken Sept. 13, 1938, showing left bundle branch block.

(Fig. 3) at this time showed that the bundle branch block was not present. Another electrocardiogram was taken Oct. 27, 1942 (Fig. 4), and again June 12, 1943 (Fig. 5), and both were the same as that of Oct. 3, 1942 (Fig. 3).

DISCUSSION

In this case the left bundle branch block followed acute coronary occlusion. There have been no reported exceptions to the observation

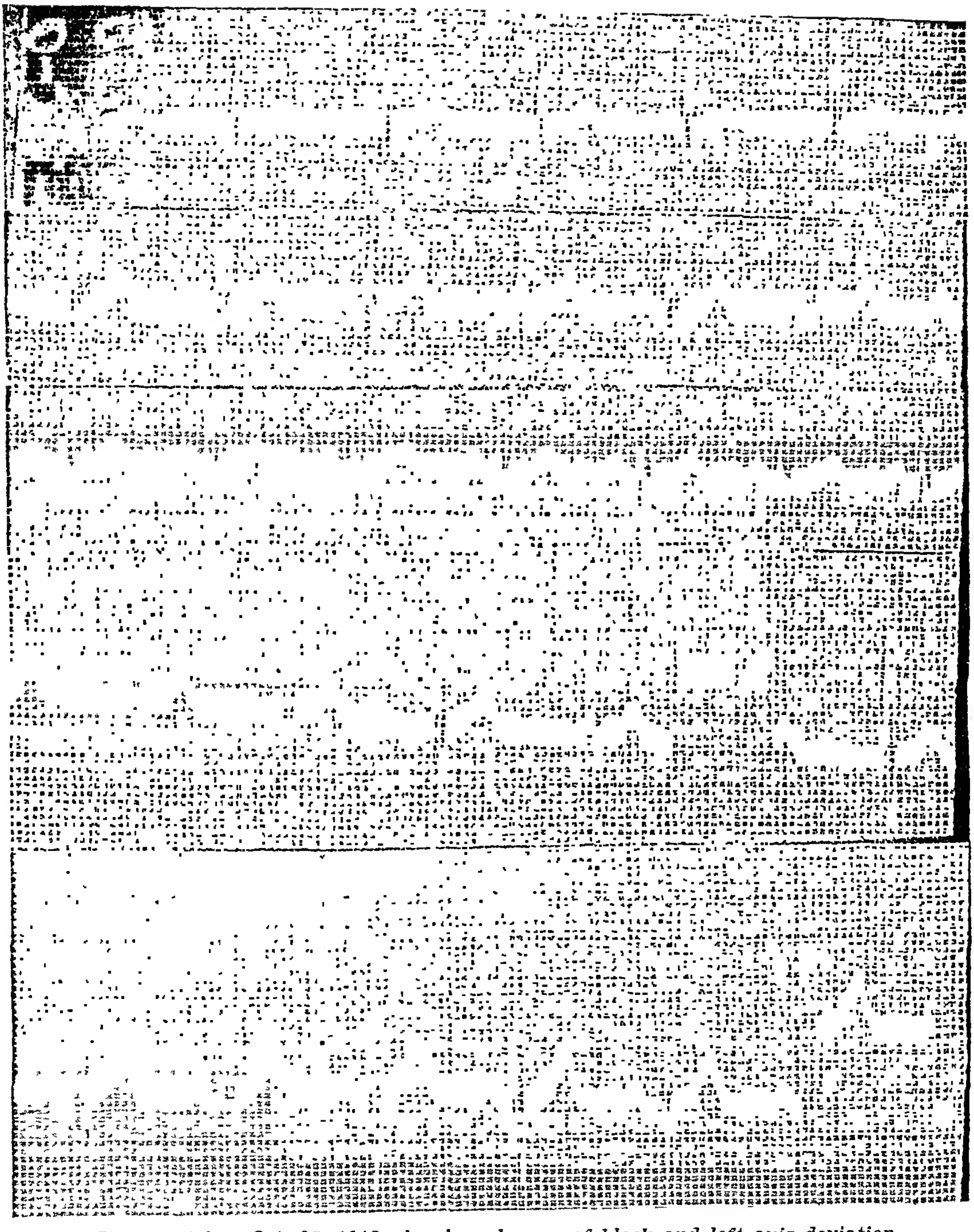

Fig. 4.—Taken Oct. 27, 1942, showing absence of block and left axis deviation.

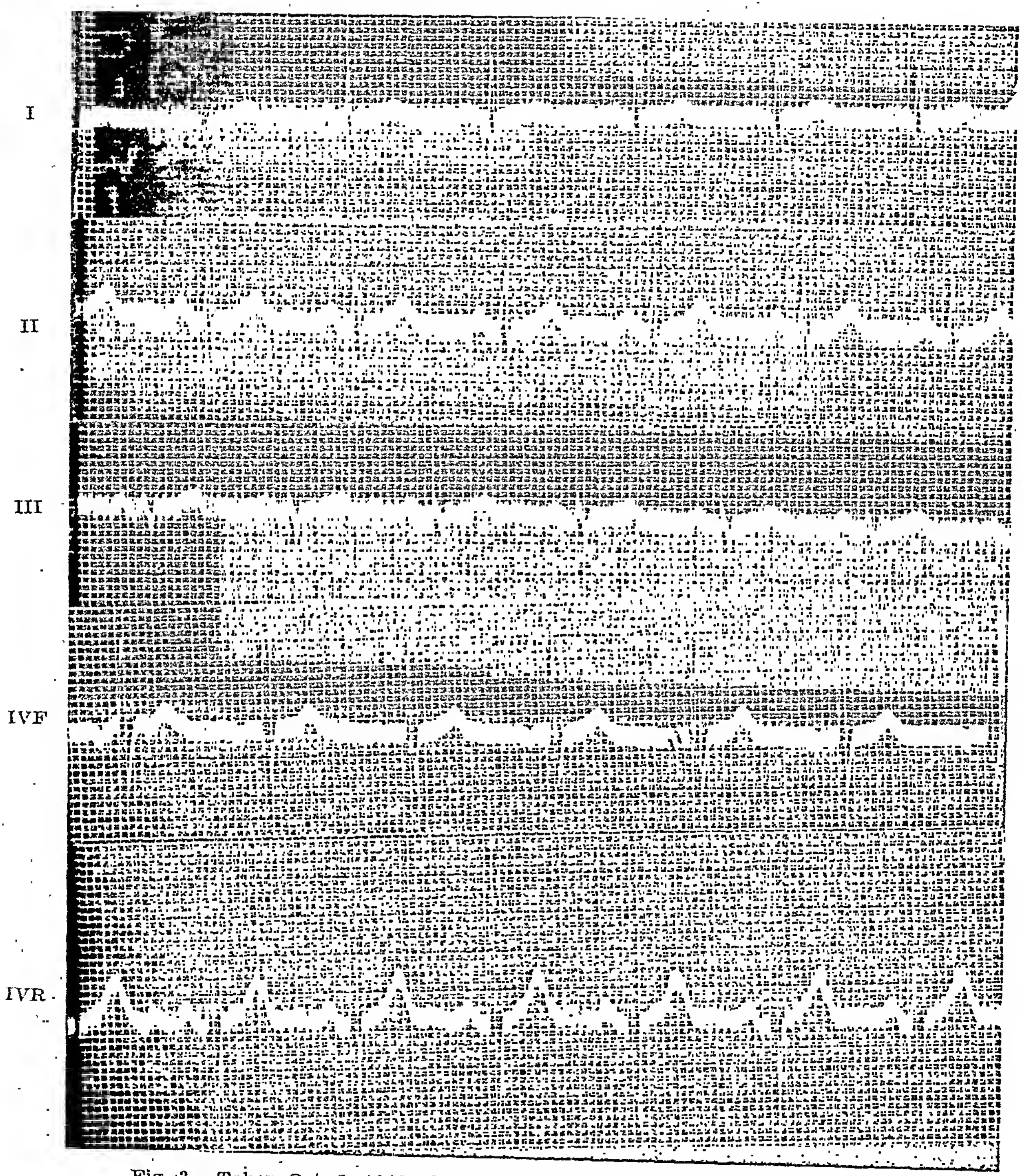

Fig. 3.—Taken Oct. 3, 1942, showing absence of block and left axis deviation.

SUMMARY

A case of bundle branch block following coronary occlusion is presented, in which spontaneous disappearance of the block occurred after a period of about four years. No similar case of persistent block which disappeared after so long an interval has been found in the literature. The case is of particular interest because the patient remained symptom free throughout the period of observation. In the presence of the bundle branch block, and in the transition to normal QRS complexes, no variations in symptoms or physical signs were apparent. This interesting paucity of symptoms parallels the case of Willius and Anderson,[4] as well as that of Bishop.[3]

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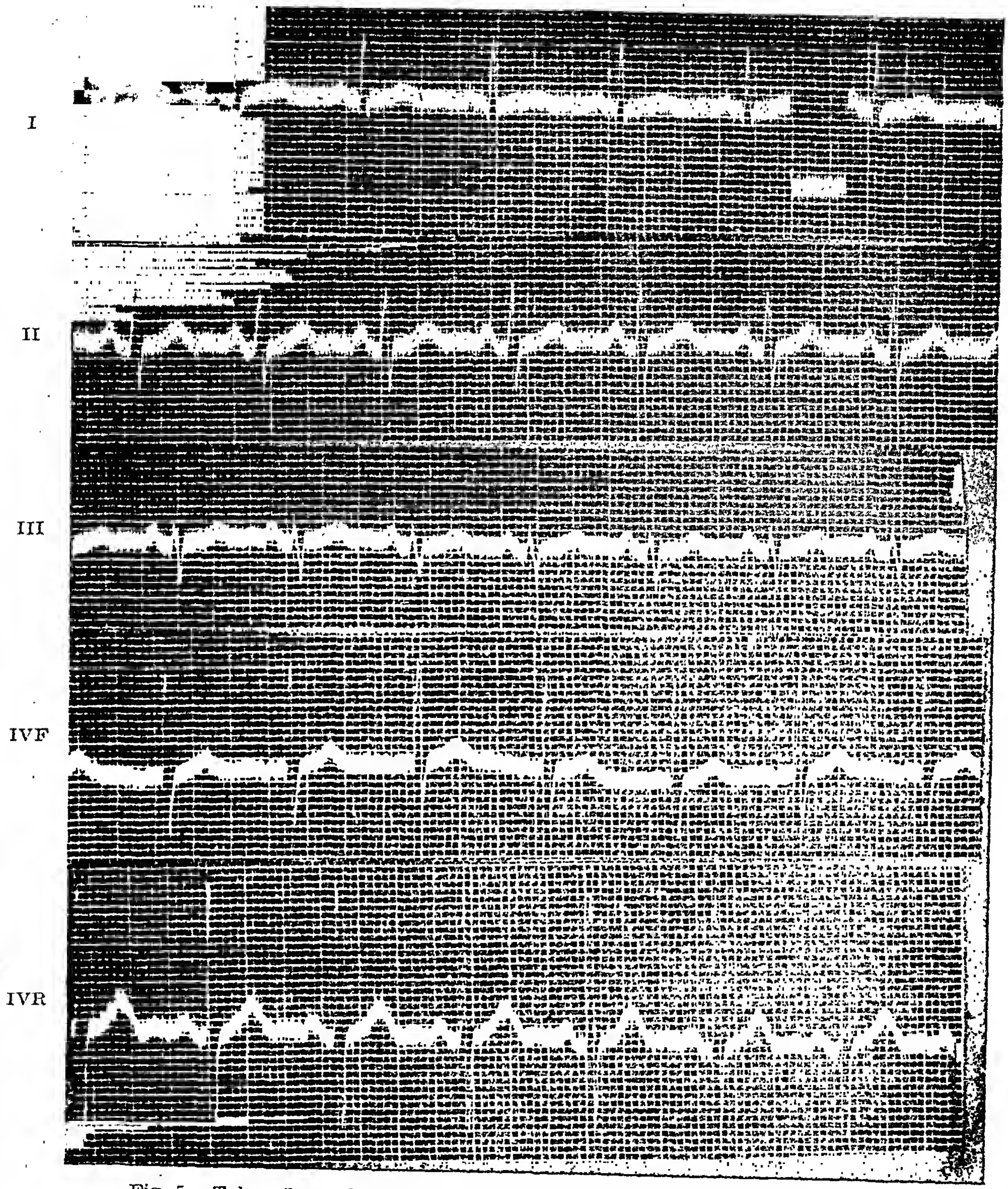

Fig. 5.—Taken June 12, 1943, showing absence of block and left axis deviation.

Kugel[3] states that he has observed two cases in adults in which the lesions were similar to those in his group of infants. Levy and Rousselot[7] reported three cases of cardiac hypertrophy of unknown origin in adults. Later,[8] one case was discarded because it could possibly have been von Gierke's disease, but eight other similar cases were added to the series. No apparent cause for the myocardial disease and enlargement could be demonstrated. There were eight males and two females, ranging in age, at death, from 26 to 66 years; symptoms of decompensation had been present from ten days to five years. In six of the cases there was some myocardial necrosis or fibrosis, and mural thrombi, with emboli to other organs, were conspicuous. Two patients had positive complement fixation tests for syphilis, although no evidence of syphilitic tissue changes could be demonstrated. In no case was there any generalized arteriolar sclerosis to indicate previous hypertension. Reisinger and Blumenthal[9] reported five similar cases, in four of which there were positive Wassermann reactions, and they considered the etiological relationship of syphilis to myocardial disease. Two other cases in adults, but without serologic or other evidence of syphilis, have been reported in the Case Records of the Massachusetts General Hospital.[10, 11]

In view of the paucity of literature concerning cardiac hypertrophy without recognized cause in older children, we record the following case.

Case CM—5715.—An 11-year-old schoolboy was examined three hours after death. He was said to have been a normal, healthy child. At the age of 2 years a broken leg was treated without complication. He had measles and chicken pox during early childhood, but no other illnesses. His progress in school was satisfactory. He performed ordinary exercises in the gymnasium, rode a bicycle, and played with other children without any apparent difficulty. On the day of death he arose, ate breakfast, and went to school as usual. While sitting at his desk during the morning class he started to rise suddenly from his seat, cried out, and fell to the floor, striking the right frontotemporal region of his head upon a desk. He appeared comatose and cyanotic, and was dead a few minutes later.

Post-mortem Examination.—The body was that of a fairly well-nourished and well-developed white male child; height, 4 feet, 5½ inches; weight, 80 pounds. There was cyanosis of the lips and fingernails.

There was a small, linear fracture of the right temporal bone, with slight hemorrhage along the fracture line. The ventricle of the brain contained bloodtinged fluid, and there were a few punctate areas of hemorrhage in the medulla near the floor of the fourth ventricle; otherwise, the brain substance was without evident lesion. The thymus weighed 45 grams, and there were scattered punctate areas of hemorrhage beneath the capsule.

The heart weighed 430 grams, and there was marked concentric hypertrophy of the left ventricle with only slight hypertrophy of the right ventricle. None of the chambers were dilated. The myocardium appeared uniformly pale and firm, and the markings of the muscle bands

CARDIAC HYPERTROPHY OF UNKNOWN CAUSE

Report of a Case

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Hypertrophy of the heart occurs as a result of some physiologic or pathologic disturbance. In most instances, the mechanism is apparent. There have been, however, a group of cases of myocardial hypertrophy for which no definite cause has been demonstrated. In most of these, the hypertrophy has been associated with endocardial fibrosis and varying degrees of myocardial degeneration, and has occurred in infants and children up to 4 years of age.[1-4] Various theories have been postulated to account for the changes; these include intrauterine infection during the early days of life, "congenital weakness of the germ plasm,"[1] and allergic reaction to milk in a heart which was already damaged by infection.[2] Kugel[3] has spoken of these as cases of "non-suppurative myocardial degeneration with dilatation and hypertrophy." Similar cases have been reported in which hypertrophy and endocardial fibrosis occurred without myocardial degeneration.[1, 5]

There are few reports of obscure cardiac enlargement in older children and adults, probably because of the multiplicity of physiologic or pathologic disturbances which occur with age and might more readily account for the changes within the organ. Whittle[6] reported one case of an apparently well-developed 20-year-old student who fell from his bicycle and died within a few moments. Post-mortem examination revealed a markedly hypertrophied heart, weighing 840 grams. The valves, endocardium, and coronary arteries appeared normal. The aorta was somewhat small and delicate, and measured 16 mm. in diameter at the commencement of the descending portion. There were no other congenital anomalies. The only additional gross abnormalities were an acute tracheitis and a persisting thymus gland, weighing 30 grams. Histologic study of the heart showed swelling and loss of striation of the muscle fibers, with no foci of inflammation or necrosis. All of the other organs appeared normal. The author felt that neither the narrowed aorta nor the persistent thymus could have accounted for the marked cardiac enlargement, although the acute tracheal infection might have been responsible for the cloudy swelling of the myocardial fibers. He postulated that prolonged muscular exertion of cycling might have played an important factor.

From the Department of Pathology, Syracuse University College of Medicine.
Received for publication Sept. 9, 1943.

no areas of degenerative change in sections stained with hematoxylin and eosin. The large and small vessels of the heart appeared normal, and there was no perivascular cellular infiltration. The endocardium and subendocardium were not thickened. Fat stains and Masson and Heidenhain stains did not contribute anything. Best carmine stains for glycogen on alcohol-fixed myocardium showed some areas with numerous, moderate to fine, red droplets, located, for the most part.

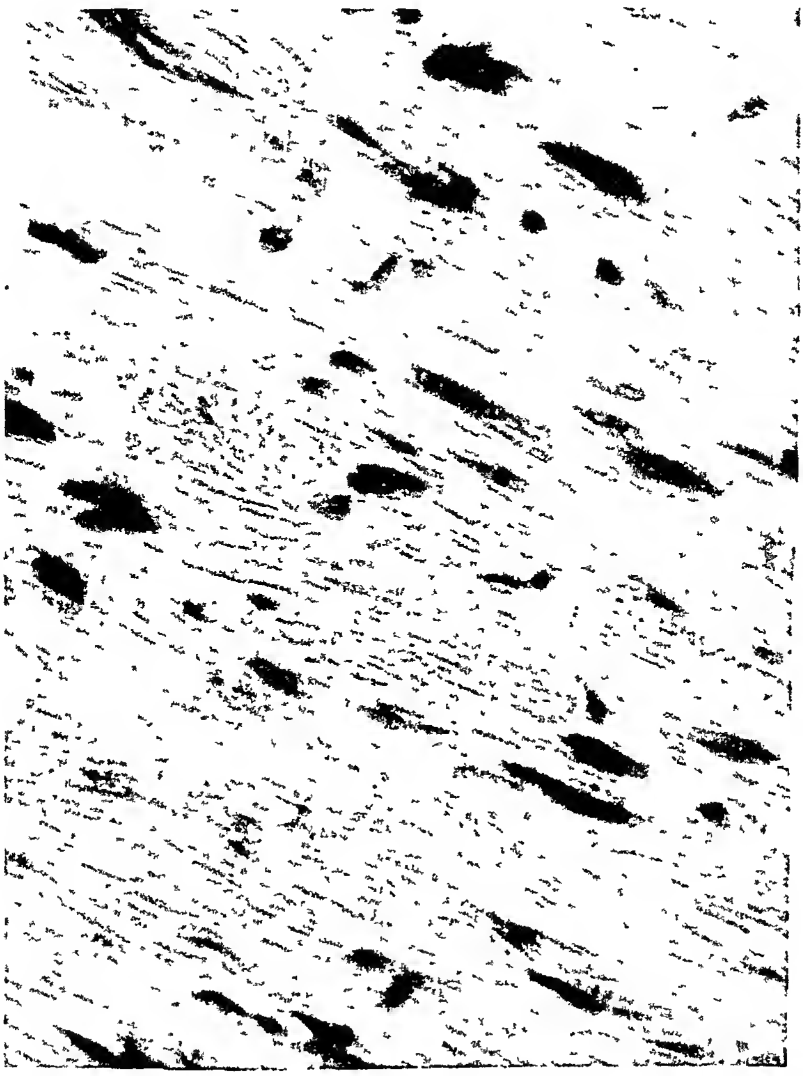

Fig. 2.—Heart muscle; idiopathic hypertrophy showing glycogen stain without droplets (×710).

within the fibers, although some were in connective tissue between the fibers. Some of these fine droplets were located transversally, like striations, across the myofibrils (Fig. 1). Other areas showed the same marked hypertrophy of the muscle bundles, but no glycogen deposits (Fig. 2). In no place did the enlargement of the muscle fibers appear to be the result of glycogen accumulation.

Quantitative analysis of the myocardial glycogen by hydrolysis and the Benedict micro method[12] showed 0.16 per cent glycogen, as contrasted with a normal of 0.07 per cent Best carmine stains of the kid-

stood out distinctly. The wall of the left ventricle measured up to 3.5 cm. in thickness. There was a reduplication of the left cusp of the pulmonary valve; the fourth cusp appeared rather small, and showed some fenestration along the free margin. Otherwise, the valves and remaining endocardium were without evident lesions. The foramen ovale and ductus arteriosus were closed. The coronary ostia were normal in size and location; the vessels throughout were patent, and showed no intimal sclerosis. There was no narrowing of the aorta or of any of the great vessels arising from it.

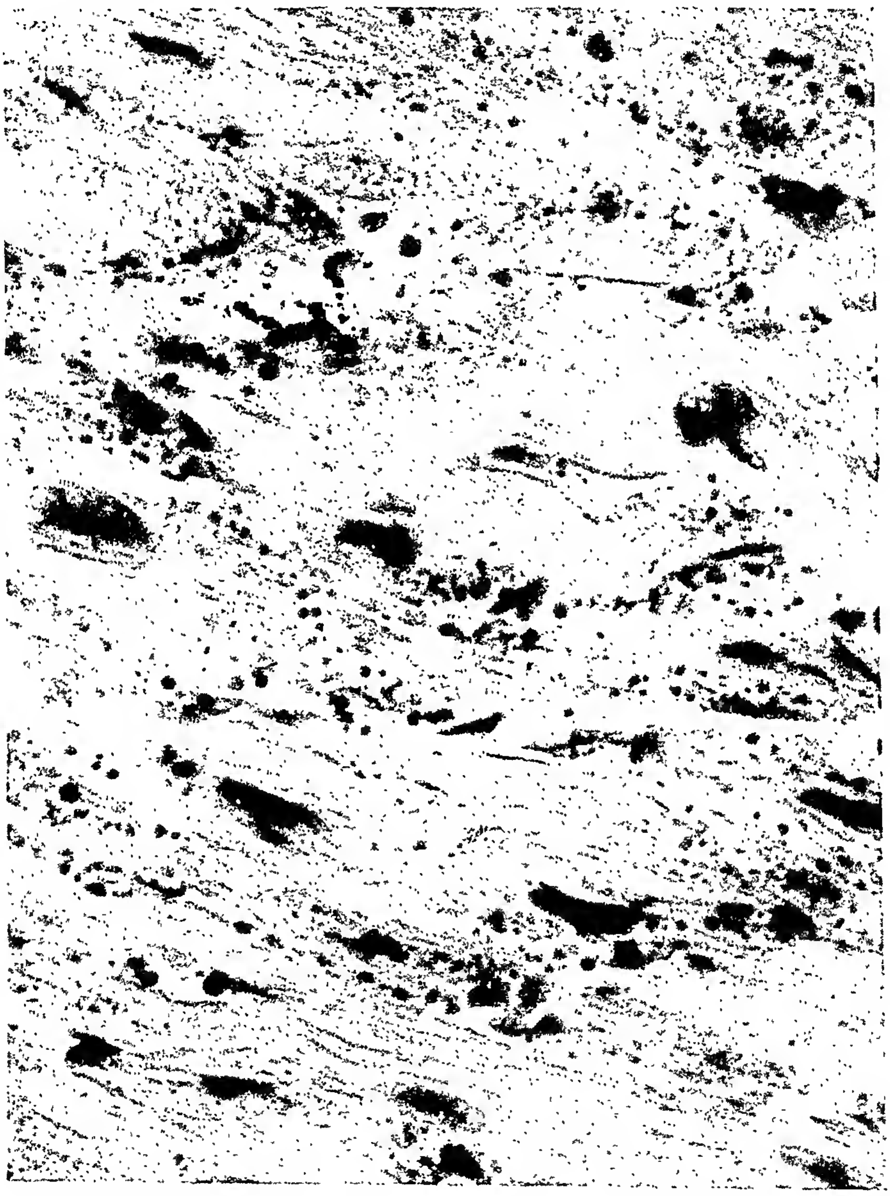

Fig. 1.—Heart muscle; idiopathic hypertrophy showing glycogen stain with droplets (×710).

The other organs showed no noteworthy changes.

Microscopically, the brain showed some edema. There was hyperplasia of the thymus, with rather numerous polymorphonuclear leucocytes in the pulp. The liver, kidneys, lungs, and other organs appeared to be entirely without evident lesion. There were no vascular changes.

There was marked hypertrophy of the muscle fibers of the myocardium, with very slight diffuse increase in fibrous tissue between the muscle bundles. There was no vacuolization of the muscle fibers, and

6. Whittle, C. H.: "Idiopathic" Hypertrophy of the Heart in a Young Man, Lancet 216: 1354, 1929.
7. Levy, R. L., and Rousselot, L. M.: Cardiac Hypertrophy of Unknown Etiology in Young Adults, Am. Heart J. 9: 178, 1933.
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9. Reisinger, J. A., and Blumenthal, B.: Myocardial Degeneration With Hypertrophy and Failure of Unknown Cause, Am. Heart J. 22: 811, 1941.
10. Case Records of the Massachusetts General Hospital (Case 26401), New England J. Med. 223: 547, 1940.
11. Case Records of the Massachusetts General Hospital (Case 28042), New England J. Med. 226: 158, 1942.
12. Hawk, P. B., and Bergeim, O.: Practical Physiological Chemistry, Philadelphia, 1937, P. Blakiston's Son and Company, Inc., pp. 436.
13. Gardner, E., and Simpson, K.: Sudden Death From Von Gierke's (Glycogen) Disease, Lancet 234: 659, 1938.

ney showed no evidence of glycogen. The liver did not contain an abnormally large amount of glycogen; chemical analyses of these tissues were not made.

COMMENT

It is of interest to note the clinical and gross pathologic similarities between this case and the one reported by Gardner and Simpson[13]; their patient was an 11-year-old, apparently healthy schoolboy who suddenly collapsed and died while playing in the street. Post-mortem examination revealed a heart which was very greatly enlarged, weighing 384 grams, due chiefly to thickening of the left ventricle. No congenital anomaly was recorded. All other organs appeared normal. Histologic study showed imperfect transverse and longitudinal striations of the heart muscle fibers due to a "pale foaminess." This appearance was the result of abnormal deposition of glycogen, as demonstrated by the Best carmine stain. The liver showed a similar, but less marked, change. No quantitative chemical studies were made, but the authors stated that the cardiac enlargement was due to glycogen disease.

In our case it is felt that the moderate increase in myocardial glycogen was possibly physiologic and commensurate with the degree of cardiac hypertrophy. At least it can be definitely stated that the increase in the size of the heart was not accounted for by increase in glycogen, as shown in the sections or by chemical analysis. The cause of the hypertrophy was not found; certainly none of the usual factors can account for it. There was no vascular evidence of prolonged hypertension. The absence of scarring or myocardial degenerative changes is evidence against previous rheumatic, diphtheritic, and other infections or "toxic" causes of heart disease. The presence of a four-cusped pulmonary valve could not have been significant, and no other anomalies were found. To consider the "congenital idiopathic" type [1,5] does not help, and no other etiological factors are apparent. It is remarkable that such marked hypertrophy could exist without some evidence of circulatory embarrassment before sudden death.

SUMMARY

A case of sudden death in an apparently healthy, 11-year-old schoolboy is presented. Marked cardiac hypertrophy was found at autopsy. The cause of the hypertrophy was not discovered.

REFERENCES

1. Kugel, M. A., and Stoloff, E. G.: Dilatation and Hypertrophy of the Heart in Infants and Young Children, Am. J. Dis. Child. **45**: 828, 1933.
2. Mahon, G. S.: Idiopathic Hypertrophy of the Heart With Endocardial Fibrosis, Am. Heart J. **12**: 608, 1936.
3. Kugel, M. A.: Enlargement of the Heart in Infants and Young Children, Am. Heart J. **17**: 602, 1939.
4. Weisman, S. J.: Congenital Idiopathic Cardiac Hypertrophy, Arch. Path. **33**: 365, 1942.
5. Powers, G. F., and Le Compte, P. M.: Remarks on a Case of Congenital Idiopathic Hypertrophy of the Heart, J. Pediat. **13**: 760, 1938.

This factor determines the size of the infarct that follows the obstruction of any given vessel and whether or not a recurrence of the episode is to be expected. The varying condition of the coronary arteries is probably the cause of the great variation in the expectation of life after myocardial infarction—a variation from a few moments to some fifteen years.

A knowledge of the behavior of diseased coronary vessels is essential in discussing the surgical procedures advocated for improving the myocardial blood supply in coronary artery disease. These procedures aim at establishing new anastomotic channels between extracardiac and cardiac arteries by placing intercostal muscles or omentum in contact with the pericardium. It is assumed in these procedures that the arterial pressure gradient will force blood from the extracardiac to the cardiac vessels. There is, however, no guarantee that such a gradient will exist. In those cases generally suitable for operative interference the one deficient in blood supply will frequently be deep in the ventricular wall. It is then very doubtful if a satisfactory pressure gradient will exist to transfer any quantity of blood to the heart, and it is possible that the flow will be in the opposite direction. This unpredictable factor probably causes the very variable results that follow these surgical procedures.

AUTHORS.

Stokes, W.: Nicotinic Acid in the Treatment of Angina Pectoris. Brit. Heart J. 6: 157, 1944.

Changes in the electrocardiogram of cardiac ischemia in man, following the administration of nicotinic acid, suggest that the drug can improve coronary blood flow; but this only results from a dosage large enough to produce peripheral flushing, which in itself is an uncertain and unpleasant effect.

In a controlled clinical trial no improvement resulted from the oral administration of nicotinic acid in moderate dosage, either in the prevention or relief of angina, and nicotinamide in larger doses failed to give better results.

Once again glyceryl trinitrate has shown that it has no equal in the treatment of angina pectoris, and nicotinic acid has no claim to routine use in this complaint.

AUTHOR.

Levine, S. A., and Likoff, W. B.: Some Notes on the Transmission of Heart Murmurs. Ann. Int. Med. 21: 298, 1944.

Numerous simple questions concerning the production and propagation of murmurs remain unanswered.

We believe that the velocity of blood flow through the cardiac chambers and great vessels is one important factor in the production of murmurs and in determining their intensity.

Other factors, such as the amount of residual blood in cardiac chambers, the proximity of the heart and great vessels to the chest wall, and the respiratory cycle may influence the presence or absence of murmurs.

The gradation of systolic murmurs from 1 to 6 is important in attempting to estimate their significance, for those of grade 3 intensity, or louder, are never observed in normal individuals, whereas those of grade 1, and occasionally grade 2, are found where there is no evidence of cardiac or other disease.

The detection of murmurs over the olecranon process even with the blood pressure cuff inflated above the systolic pressure level, proves that murmurs are transmitted through bone.

The transmission of an aortic diastolic murmur to the skull, and of the systolic murmur of ventricular septal defect to the carotid area proves that murmurs are not propagated with the blood stream, for the blood flow in these circumstances is in the opposite direction.

Abstracts and Reviews

Selected Abstracts

Rotta, A.: Weight of the Heart and Number of Cardiac Capillaries in Guinea Pigs at Different Altitudes. Rev. argent. de cardiol. **10:** 186, 1944.

A study was made of the heart weight in relation to body weight in guinea pigs born or acclimatized at different altitudes in order to ascertain whether chronic anoxia produces myocardial hypertrophy. In the same animals, the cardiac capillaries per millimeter were counted, and the average diameter and the area of myocardial fibers were measured. The results were compared with identical determinations made in animals living at sea levels.

Chronic anoxia produces some degree of cardiac hypertrophy at altitudes over 3,700 meters. Below this level the heart weight does not differ from that at sea level. At 4,500 M. the heart weight is 30 per cent greater than that at sea level, no difference being observed between native and acclimatized animals. There seems to be a close relationship between severity of anoxia and degree of hypertrophy.

In the cardiac hypertrophy of altitudes the number of cardiac capillaries diminishes as the thickness of the fibers increase, the same as in clinical hypertrophy. The average diameter and the area of myocardial fibers increase together with the increase in heart weight.

AUTHOR.

Palatucci, O. A., and Knighton, J. E.: Short P-R Interval Associated With Prolongation of QRS Complex; A Clinical Study Demonstrating Interesting Variations. Ann. Int. Med. 21: 58, 1944.

Four cases are reported, exhibiting the syndrome of short P-R interval associated with prolonged QRS complexes in patients with apparently undamaged hearts. Features in common with previously described cases are enumerated. All the variations ascribed to this syndrome are demonstrated, except reversion to normal rhythm after digitalis and quinidine.

Paradoxical atropine effects, a ventricular extrasystole, and recovery from auricular paroxysmal tachycardia are recorded.

Spontaneous and atropine induced T-wave changes are emphasized.

AUTHORS.

Lowe, T. E., and Wartman, W. B.: Myocardial Infarction. Brit. Heart J. **6:** 115, 1944.

Many of the indications of the existence of a myocardial infarct have a ready explanation. Fall of arterial blood pressure is in most cases due either to the amount of muscle tissue destroyed or to the particular muscle involved. Abnormalities in cardiac rhythm and the electrocardiographic changes will be better understood when sufficient data have been compiled relating to the problems of the electrical activity of the heart. Accurate localization of the specific muscle bundles involved may enable us to predict when rupture of the ventricles or even when congestive cardiac failure is to be expected.

The prognosis of a case of myocardial infarction depends as much upon the disease causing the arterial block as it does upon the extent of the muscle damage.

Taylor, F. R., and Morehead, R. P.: Spontaneous Complete Rupture of the Aorta Without Dissecting Aneurysm, With Report of a Case Showing a New Physical Sign (Periaortic Friction Rub). Ann. Int. Med. 21: 81, 1944.

Rupture of the aorta is by no means infrequent in the anatomic, as well as the pathologic and clinical literature.

It occurs without the formation of a dissecting aneurysm more often than is usually realized, though the cases with dissecting aneurysm are much more numerous.

The literature on the type of rupture occurring without dissecting aneurysm has been reviewed and an additional case of our own presented, with clinical and pathologic findings.

The gross and microscopic pathology of the condition is discussed.

Certain diagnostic criteria, including a hitherto undescribed physical sign, have been suggested.

The prognosis is hopeless, and treatment is purely symptomatic.

AUTHORS.

Blumenthal, H. T.: Calcification of the Media of the Human Aorta and Its Relation to Intimal Arteriosclerosis, Ageing, and Disease. Am. J. Path. 20: 665, 1944.

The frequency of occurrence and the influence of age, sex, and disease on calcification of the media of the human aorta were studied by means of sections prepared by hematoxylin and eosin staining and by microincineration. The results showed that calcification of the media precedes the formation of intimal plaques; that intimal plaques do not occur without calcification of the media or other medical change such as syphilitic aortitis, or marked connective tissue infiltration of the media; and that within a single aorta medial calcification is probably more intense in the immediate vicinity of an intimal plaque than elsewhere. In a few observations it was noted also that calcification of the human aorta was more pronounced in the abdominal than in the thoracic portion of the aorta.

Calcification of the media of the aorta was shown to be primarily a function of age and was not influenced by sex and various chronic infectious diseases. However, specimens from hypertensive persons between the ages of 30 and 60 years showed considerably more medial calcification than did the "controls." Of 42 cases of syphilitic aortitis, 33 showed no medial calcification, and 9 showed only slight calcification of the media.

The relationship between calcification of the media of the human aorta and the loss of elasticity and contractility with age, as well as the possible relationship of these changes to the formation of intimal plaques, is discussed.

AUTHOR.

Weinstein, J.: "Atypical" Coronary Disease in Young People. Ann. Int. Med. 21: 252, 1944.

Ten cases presenting cardiac manifestations and characteristic electrocardiographic variations suggestive of an unusual type of cardiac infarction are presented.

The patients ranged in age between 20 and 37 years, the average being 28.4 years; 60 per cent of the group were Negroes.

All cases gave a history of upper respiratory infections; four of the cases had joint disturbances; five of eight of the cases had high autistreptolysin titers. None had leucocytosis or polynucleosis, but all had rapid red cell sedimentation rates.

The electrocardiographic variations were characterized by T-wave changes with both anterior and posterior wall type of localization, occasional RT changes, and the consistent absence of QRS abnormalities.

Systolic murmurs after effort occur in normal individuals. The production or accentuation of such murmurs after exercise, therefore, cannot be used as a diagnostic test.

There are several mechanisms involved when murmurs are influenced by respiration. All faint murmurs, organic or functional, may disappear with a deep inspiration. In some instances extracardiac systolic murmurs may be louder, and in others fainter, with a deep expiration.

The current teaching about propagation of murmurs needs revision.

These considerations are important in the examination of selectees for military service.

AUTHORS.

de los Reyes, R. P., de la Torre, H., Labourdette, J., and Junco, J. A.: Rheumatic Cardiopathies in Cuban Children. Arch. de med. inf. 13: 3, 1944.

The authors refer to the incidence and importance of rheumatic cardiopathy among Cuban children, which, though relatively less numerous than in the cold countries, constitutes the greatest calamity children's hearts suffer with acquired cardiopathies.

The study is based on 100 children, 50 boys and 50 girls, chosen from among 200 clinical records of rheumatic children which have been followed up for a long time with a series of electrocardiographic and orthodiagraphic studies, sedimentation rates, and other complementary investigations, pointing out the lesional diagnosis, course of the disease, and treatment used, plus an anatomopathologic study of post-mortem examinations.

The authors have found 30 per cent more incidence in the girls than in the boys; the ages ranged from 5 to 11 years, inclusive. The white race was attacked most often, then the Negro, and third, the mulatto. The poorer and most needy classes offer the greatest number of cases. Mortality has been found to reach 18 per cent.

AUTHORS.

Peete, D. C.: Rheumatic Fever: Diet as a Predisposing Factor. Ann. Int. Med. 21: 44, 1944.

The author relates evidence which indicates that diet and sunshine are the most important predisposing factors in the causation of acute rheumatic fever. He discusses various climatic conditions which are related.

He believes that the dietary deficiency which closely follows the incidence of clinical rickets alters the individual's immunity to the organism which produces the clinical picture of acute rheumatic fever.

MCCULLOCH.

Rodbard, S., and Katz, L. N.: The Effect of Pregnancy on Blood Pressure in Normotensive and Hypertensive Dogs. Am. J. Obst. & Gynec. 47: 753, 1944.

The blood pressure in normotensive and especially in hypertensive dogs tends to fall late in pregnancy. The degree of reduction of blood pressure is apparently affected by the size of the litter.

It is possible that the blood pressure decline is related to the low resistance placental circuit which develops during pregnancy. It is also possible that some humoral factor (not involving the fetal kidneys) caused by the maternal endocrine alterations which accompany pregnancy contributes to the blood pressure change and helps to account for the variability in the time at which this blood pressure drop occurs.

Surgical or other traumatic intervention during the latter part of pregnancy appears to predispose to abortion in the dog.

AUTHORS.

Rhode, C. M.: Studies on the Effects of Posture in Shock and Injury. Ann. Surg. 120: 24, 1944.

The effect of postural change on thirty patients with various degrees of injury is described.

Vasomotor instability was demonstrated in injured patients; this was not present in normal controls and disappeared in injured patients when they returned to normal.

Different effects were noted in response to the head-up or the foot-up position in mild and severe injury or hemorrhage.

Some of the beneficial effects of the foot-up position in the treatment of shock or potential shock as well as some of the adverse effects observed in injured patients in the head-up position are described.

AUTHOR.

Beck, C. S.: Operation for Aneurysm of the Heart. Ann. Surg. 120: 34, 1944.

The author describes an operation for repair of aneurysm of the left ventricle of the heart. The operation consists of grafting a segment of fascia lata or perietal pericardium over the aneurysm for the purpose of preventing its rupture. The purpose of this procedure is the deliberate reduction of cicatrix to support a dilating heart and also to prevent rupture of an aneurysm of the heart.

MCCULLOCH.

Neuhof, H.: Infected Dissecting Aneurysm of the Iliac Artery Following Arteriovenous Fistula of the Femoral Vessels. Ann. Surg. 120: 41, 1944.

Severe grades of dilatation of the proximal artery in cases of arteriovenous aneurysm of the popliteal or femoral vessels should be treated by excision of the dilated artery. In the presence of infection within the ectatic artery, excision is imperative.

AUTHOR.

Schindel, L. E., and Braun, K.: The Place of Foliandrin Within the Group of Cardiac Glucosides. Brit. Heart J. 6: 149, 1944.

The pure glucoside foliandrin isolated from the Palestinean oleander bush (*Nerium oleander*) distinguishes itself very definitely from principles so far isolated from various oleander species. Apart from other chemical as well as physical characteristics, it could be shown by means of continuous electrocardiographic tracings from a cat's heart, that upon intravenous administration its action is identical with that of the principles belonging to the group of strophanthin (ouabain) gluco sides and the drug should therefore be considered a ''strophanthinoid.'' In contradistinction to strophanthin, it displays its full cardiac activity upon peroral administration.

AUTHORS.

Deyrup, I. J.: Circulatory Changes Following the Subcutaneous Injection of Histamine in Dogs. Am. J. Physiol. 142: 158, 1944.

Subcutaneous injection of 3 to 12 mg. histamine base per kilogram in unanesthetized and etherized dogs resulted in a characteristic circulatory disturbance which differed markedly from traumatic shock in the clinical symptoms produced, in the far greater hypotension, and in the absence of definite blood volume reduction as an etiological factor. Change in blood volume in histamine shock under these conditions resulted from a moderate increase or decrease in plasma volume, and increase in calculated red cell volume, which may have resulted from mobilization of cells from the spleen and other blood depots.

AUTHOR.

All the cases improved clinically. The electrocardiograms reverted to a normal pattern in six of the cases and in three the changes improved considerably with the probability that they would in time revert to normal.

The upper respiratory infections, the occasional joint disturbances, and the high antistreptolysin titers suggest a rheumatic type of infection.

There is general agreement on the occurrence of coronary arteritis in rheumatic infections. Acute inflammatory arteritis characterized by fibrinoid degeneration and late fibrotic changes has been demonstrated. Cases of our series fit into both types clinically.

AUTHOR.

Lewes, D.: Pulmonary Embolism: The Clinical and Cardiographic Progress of a Case. Brit. Heart J. 6: 161, 1944.

A case of pulmonary embolism with acute cor pulmonale is described. A severe degree of cor pulmonale developed in the absence of radiological evidence of pulmonary infarction.

Emphasis has been placed on the value of triple rhythm, from the addition of the third heart sound, in the diagnosis of suspected cases of pulmonary embolism.

Radiographic evidence of distension of the right auricle and right ventricle is related to the onset and duration of the cardiographic changes. Inversion of the T wave in CR_1 is probably the most sensitive of the cardiographic indices of right ventricular failure. The value of this change and of findings in lead CR_7 in the diagnosis of acute cor pulmonale from posterior cardiac infarction is confirmed.

AUTHOR.

Brown, J. W., and Hampson, F.: Temporal Arteritis. Brit. Heart J. 6: 154, 1944.

A case has been described in which the clinical and pathologic findings are those of an arteritis of the temporal arteries. Perusal of the reports of similar cases suggests that temporal arteritis is but a local manifestation of a general disease of the arterial tree.

AUTHORS.

Smith, C. C., Zeek, P. M., and McGuire, J.: Periarteritis Nodosa in Experimental Hypertensive Rats and Dogs. Am. J. Path. 20: 721, 1944.

Periarteritis nodosa was found at autopsy in twenty-six of sixty-two rats and four of eight dogs which had been made hypertensive by wrapping their kidneys with silk. No evidence of these lesions was found in groups of control animals.

In animals presenting periarteritis nodosa at autopsy, the monthly mean blood pressure levels had been higher than in animals in which no periarteritis nodosa was found. This higher level had been manifested within one month after the production of perinephritis and had been maintained throughout the six months of observation.

Suppurative lesions were common in the experimentally produced perinephric membranes.

A review of the literature revealed no report of the occurrence of periarteritis nodosa in animals in which the kidneys and the blood pressure were proved to be normal.

In the present series of hypertensive animals the two observed differences between those which had and those which did not have periarteritis nodosa were, in the former: higher mean blood pressure levels, and more frequent and more extensive suppurative lesions around the kidneys.

AUTHORS.

PHYSIOLOGY IN HEALTH AND DISEASE: By Carl J. Wiggers, M.D., D.Sc., Professor of Physiology, School of Medicine, Western Reserve University. Fourth edition, Lea & Febiger, Philadelphia, 1944, 1174 pages, 247 illustrations, $10.00.

The editors of the AMERICAN HEART JOURNAL asked the reviewer to cover only the part of this well-known textbook which is concerned with cardiovascular physiology, to which Section V, which comprises 285 pages, is devoted.

Dr. Wiggers' many investigations in this field are well known, and a careful summary of this work, together with his views on the work of others, is given. The contents have been brought rigorously up to date, over 1,000 new references have been added, and especial attention has been given to topics, such as shock and hemorrhage, brought to the front by the war. Although some material previously included has been omitted to save space, the omissions have been well chosen. The style is perhaps somewhat obscure in places, but is usually clear and vigorous; the reviewer especially liked the analogy between the vectors whose resultant is the electrocardiogram and the efforts of two teams of men pulling in various directions upon a rope. Indeed, the reviewer read the section with no little profit to himself.

There have always been two schools of physiologic thought. The first insists on methods of the utmost refinement, but, in order to apply them, must turn to animal experiments and often be willing to sacrifice normality by the use of anesthetics and elaborate operative procedures. Inasmuch as this school possesses a strong faith in the uniformity of nature, it does not hesitate to apply the results obtained in such animal experiments to human problems. The second school prefers to solve problems related to man by working on man himself, or on animals which are disturbed as little as possible, both physiologically and psychologically. But, in order to accomplish this aim, the members of this school must be content to employ methods far cruder than those of the first group. Knowledge has been advanced by both schools.

In his philosophy of science Dr. Wiggers is a charter member of the first school, whereas the reviewer belongs to the second. Therefore, the latter would prefer to have medical students presented with less generalization from the results, and with more details concerning the situation under which observations quoted were made. In acute animal experiments, the type and depth of anesthesia, the extent and duration of the operative procedure, and the species of animal play a part in the results obtained. Although medical students taking Dr. Wiggers' laboratory course would surely realize the hazards involved in the interpretation of results obtained in such animal experiments, and although certain difficulties are pointed out in this textbook, the general tenor of the reasoning is to emphasize the method of recording, and, if this is satisfactory, to draw a conclusion which encompasses the whole mammalian field. The reviewer believes that the relation between the rising school of physiologic clinicians and the group whose lives have been devoted to elaborate animal experimentation would be sounder if the difficulties inherent in the interpretation of such experiments were given more emphasis in physiologic textbooks and in the teaching of medical students.

ISAAC STARR.

PRE-EXCITATION, A CARDIAC ABNORMALITY: By Richard F. Öhnell, translated by Ulla Schött, P. A. Norstedt & Söner, Stockholm, 1944, 167 pages, 30 illustrations.

Pre-excitation is a term used by the author to mean that the ventricular part of the heart is subjected to an additional excitatory spread, setting in shortly before the start of the regular excitation wave. This is the phenomenon reflected in electrocardiograms by the combination of a short P-R interval and a prolonged, aberrant QRS complex.

This monograph, which, it is announced, is to be published as a supplement to *Acta Medica Scandinavica*, has been excellently translated into English. The author

Book Reviews

Escleroses Valvulares Calcificadas: By Dr. Roberto Menezes de Oliveira. Tipografia do Patronato, Rio de Janeiro, 1943, 154 pages, 67 illustrations.

This excellent monograph is based on the study of one hundred cases at the Peter Bent Brigham Hospital in Boston. The first part is devoted to the anatomy and histology of the heart valves. The second part is a pathologic study of calcification of the cardiac valves, with a discussion of twenty-five autopsy cases. The third part comprises observations on one hundred cases from the roentgenologic point of view. The fourth part is a clinical study. A short description of the cases and an extensive summary, in both Portuguese and English, close the book.

Some of the conclusions deserve to be extensively quoted. The posterior part of the *annulus fibrosis* of the mitral valve is a frequent site of calcification. The latter, however, often appears at points of functional strain, such as the valvular insertions. Calcification of the valve ring is always accompanied by a lesion of the valve, usually of a fibrotic type. Purely degenerative lesions of the ring, on the other hand, may be more limited. Calcification of the valve ring is more common in women than in men. Degenerative, calcific lesions of the valves are almost always caused by endocarditis, but calcific lesions of the valve rings may be due to either endocarditis or arteriosclerosis.

Calcification limited to the aortic ring is rare. It may be caused by both inflammatory and degenerative lesions (either ascending or descending). It gives no signs or symptoms, and is recognized roentgenologically only with difficulty.

The differentiation between purely degenerative lesions and arrested, mild endocarditic lesions can be made only by means of serial sections, and even then may be impossible. The two lesions, moreover, may be either associated or superimposed. Impairment of cardiac conduction is rarely caused by extension of degenerative processes to the septum.

Roentgenologic diagnosis of calcification of either the valves or their rings is easy, but often incomplete. The diagnosis is more difficult in cases in which the lesions are mixed.

Data are given which can be used for the roentgenologic differentiation of calcification of the *annulus fibrosis* from that of the aortic valves. Means of differentiating, roentgenologically, between aortic and mitral valve calcification are also given.

Calcification of the mitral valve is pathognomonic of mitral stenosis only when it is limited to the leaflets, in which case it is always the result of endocarditis. Valve calcification is a sign of valvular disturbance, usually stenosis, when it is of endocarditic origin. Degenerative processes rarely disturb the function of the mitral valve, but may cause aortic stenosis.

Roentgenologic study of valvular calcification has illuminated many interesting phenomena of cardiac dynamics. Slight mitral stenosis and regurgitation were found in eleven cases, and slight aortic stenosis and regurgitation in only one case, out of twenty autopsy cases of purely arteriosclerotic, but extensive, lesions of the cardiac valves.

Excellent sketches and adequate, or good, roentgenograms are presented.

Aldo Luisada.

American Heart Association, Inc.

1790 Broadway at 58th Street, New York, N. Y.

THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The American Heart Journal is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

Annual membership is $5.00. Journal membership at $11.00 includes a year's subscription to the American Heart Journal (January-December) and annual membership in the Association. The Journal alone is $10.00 per year.

The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

**Executive Committee.*

reveals a comprehensive and accurate knowledge of the literature. He has made various types of observations on seventy cases. Perhaps the most interesting is the demonstration in one case of a "peripheral" muscular band connecting the left auricle and left ventricle. The muscle in this band appeared to be nonspecialized, and thus resembled the multiple connections between the right auricle and right ventricle found by Wood, Wolferth, and Geckeler in a case with a similar electrocardiographic anomaly. Another interesting observation is what appeared to be a familial incidence in two families.

The author concludes that the abnormality of mechanism in most cases is that suggested by Wolferth and Wood, in 1933, to the effect that the cardiac behavior could be accounted for by assuming that the excitatory process is transmitted from auricles to ventricles via *both* the normal channels and an accessory conduction tract. He believes, however, that, in certain cases, the abnormality may be acquired, and that mechanical stimulation of a ventricle by auricular activity might be the underlying mechanism.

This monograph is unhesitatingly recommended to all who are interested in the anomaly of short P-R interval and prolonged aberraut QRS complex. The only serious criticisms this reviewer has to make are as follows: (1) The method of presentation, by which, in each of the nineteen chapters, all with a summary, a single aspect of the subject is discussed, leads to much repetition. (2) The author has not utilized chest leads to the fullest advantage in his study of the subject. By their use, provided the exploring electrode is placed over both the right and left sides of the precordium, the fundamental differences in mechanism between intraventricular conduction defect and this anomaly are so clearly displayed that confusion between the two would be difficult.

CHARLES C. WOLFERTH.

Erratum

On page 269 of the August, 1944, issue of THE JOURNAL, in a footnote to his review of *Hipertension Arterial Nefrogena,* Dr. Aldo Luisada stated that Professor B. A. Houssay has been working for the Rockefeller Foundation since his dismissal by the present governmental regime of Argentina. Later it was learned that Professor Houssay is working in a private institute in Argentina. Some of his collaborators have obtained apparatus and assistance through the Rockefeller Foundation.

The contemporary literature of this disease suffers from the fact that many of those who have concerned themselves with the theoretical aspects of human echinococcosis have published their observations in the foreign literature, so that much of the material is not readily available. That this is particularly true of the cardiac type of infestation is due, first, to the rarity of the condition, and, second, to the fact that it is an affliction which had only once been suspected ante mortem prior to 1905,[6] and only once definitely diagnosed before 1925.[7]

Professor F. Dévé, of France, is the figure who stands out as the authority on echinococcal disease. There is no entirely adequate summary of his work on cardiac echinococcosis in English, and much of his writing is not easily obtainable. Thus it seems wise at this time to allow the diagnosis of a case of cardiac echinococcosis to serve as the basis for a discussion of the subject. Arce's papers[2] on hydatidosis have recently offered an excellent background for the study of the more common forms of the disease.

In our analysis of the literature we have collected fifty-six of the at least seventy-five reported cases of cysts of the left side of the heart. To these we have added five cases not previously reported, including one seen by the authors at the Peter Bent Brigham Hospital in the terminal phases (Case 1).

The cases cited in this paper do not constitute all of those in the literature for two reasons, namely, the inaccessibility of certain of the articles, and the unsuitability of some of the reports for proper analysis. It has been necessary to be somewhat arbitrary in deciding whether or not to include certain cases of involvement of the cardiac septa in this series. An effort was made to include only those cases in which the left side of the heart was definitely infested.

History.—Prior to 1900, cardiac echinococcosis could be studied in the literature in numerous post-mortem reports and tabulations of such reports,[8-16] but from little else. It is true that some of those charged with the care and examination of the victims of the affliction had ventured to speculate upon the origin of the cardiac cysts and the nature of the terminal events,[6, 17] but such studies were not productive of anything more than speculation. Therefore, when Dévé, of Rouen, first as a medical student and later as a professor, began his investigations into the mechanism of echinococcal disease, particularly of possible routes of infestation and of the dissemination of the parasite within the body, he found himself working in an almost virgin field. He and his pupils remain the authors of virtually all definitive work on this disease.

The first report of cystic disease of the heart which is definitely identifiable as echinococcal dates from 1836.[18] Until the time of Dévé's thesis,[19] in 1901, the number of cases of primary involvement of the left side of the heart and the systemic circulation numbered at least thirty-five. Since then this number has been augmented by about forty more.

American Heart Journal

VOL. 29 FEBRUARY, 1945 No. 2

Original Communications

CLINICAL AND THEORETICAL CONSIDERATIONS OF INVOLVEMENT OF THE LEFT SIDE OF THE HEART WITH ECHINOCOCCAL CYSTS

A REVIEW OF THE LITERATURE, WITH A REPORT OF FIVE NEW CASES, INCLUDING ONE OBSERVED BY THE AUTHORS

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ECHINOCOCCAL disease holds a somewhat unique position in that, despite the fact that it is extremely common in some areas, it has been given close attention by a surprisingly small number of investigators. The early work on pathologic anatomy and life cycle was thorough. Although some doubt exists regarding the actual mode of transmission from animals to man,[1] hypotheses have been advanced which seem tenable in the absence of direct proof.[2, 3] Studies of the disease in man have been limited principally to case studies, statistical compilations, reviews of surgical techniques, and pathologic reports. Transmission, pathogenesis, and the mechanism of human infestation, all factors of vital importance in the understanding of any disease, have been left as the province of a small group of men in various endemic areas, and it is to them that we owe our present knowledge.

Clinical echinococcosis is predominantly a hepatic and pulmonary disease. Its surgical therapy has been extensively discussed in the world literature. This paper is concerned with the small group of cases in which the primary infection passes through the hepatic and pulmonary filters to involve the heart, and secondarily the peripheral organs. Although such cases constitute, at most, less than 2.5 per cent of total human infestations with the dog tapeworm,[4, 5] they are important and interesting to the clinician because of the challenge they present in terms of diagnosis and treatment.

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Received for publication April 3, 1944.

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ing made to do so with less success.[39] The increase in the number of diagnosed hydatids in North Americans has led Magath[33] to the belief that the disease is becoming, or has become, endemic in man in this country.

There is a definite relation of cardiac infestation to age. Dévé[25, 28] pointed out, as have others,[40, 41] that it is probable that the original infestation in human beings occurs usually in children, but that its clinical manifestations do not appear with great frequency until considerably later (except in the case of intracranial cysts) because they must attain sufficient size to cause mechanical interference with the affected organ before making themselves known. Cardiac cysts have only rarely given rise to symptoms before the age of 20 years, and the most common age for discovery is in the third and fourth decades, excepting that group of cases in which symptoms never develop and cardiac cysts are found incidentally at autopsy. Reports have been published, however, of cysts at all ages from 11 to 70 years.

The location of cardiac cysts is governed by the anatomy of the coronary arteries.[19] Because the entrance of the right coronary is more direct than that of the left, the majority of cysts are found in the right side of the heart, roughly in the proportion of 3:2.[17, 18] Since the incidence of cardiac cysts has been estimated at 0.5 to 2 per cent of all echinococcal cysts,[4, 5] the cases of involvement of the left side of the heart constitute, at most, 0.75 per cent, and more probably less than 0.5 per cent, of all cases.

The auricles are far less often affected than the ventricles.[40]

The difference between the sexes in the incidence of the disease is the same as in all echinococcal disease, with males predominating;[40] the ratio is about 2:1,[33, 40, 41] presumably because of occupational exposure.

Etiology and Pathogenesis.—The primary form of the organism is the dog tapeworm, *Echinococcus granulosus.* Dogs are infested by eating uncooked cysts, and therefore the disease predominates in stock-raising areas, particularly in sheep-grazing regions where dogs are kept for tending sheep. Magath[42] has pointed out that in America and England, where the tradition has been maintained that sheep dogs must never be allowed to feed on mutton, the disease has never flourished, whereas formerly in Iceland,[38] and at present in Australia, New Zealand, and Argentina, where such dogs are fed on uncooked offal from sheep and cattle, canine infestation and human disease are widespread.[33, 41]

The mode of transmission of the larvae from the dog intestine to human beings remains in some doubt.[1] In animals this takes place as a result of pollution of grazing grounds by dogs. Since some 70 per cent of human cysts are hepatic, it is presumed that the larvae travel by way of the digestive tract, but definite proof is difficult, if not impossible, to obtain. Dévé has suggested[25] that infestation takes place almost entirely in childhood, when association with pets tends to be most intimate,

It was early noted that the condition of these cysts of the heart varied. Originally reported as incidental autopsy observations, cases began to appear in which the rupture of cysts had obviously caused death.[8, 20, 21]

It had always been recognized that the liver was the most common site of echinococcal cysts, followed by the lungs, and that the peripheral organs were far less frequently involved. It remained for Dévé, in the early years of this century,[4, 19, 22-28] to explain the mechanisms responsible for this distribution. In 1887 a cardiac cyst was first suspected as the cause of illness prior to death,[6] but it was not until the roentgen ray came into use that the first definite ante-mortem diagnosis was made (1905[7]). Since that time, additional ante-mortem diagnoses have been reported, including one[3] in North America.

The possibility of operative removal of such cysts was suggested early, but the earliest reported attempt at such therapy that we have found was in 1921,[29] and the first successful operation was reported in 1932.[30] Removal of a peripheral embolus arising from rupture of a cardiac cyst had been reported in 1889.[13]

Since the total number of cases in which the disease was diagnosed and treated remains so small (six and two cases, respectively) it must be obvious that the history of this condition remains largely unwritten, and that evaluation of the use of newer skills in thoracic surgery will be impossible for some time to come.

Occurrence.—The geographic occurrence of hydatid disease of the heart is, as one would expect, that of echinococcosis in general. Australia, New Zealand, North Africa, Europe, Asia Minor, Argentina, and Uruguay are the areas where it originates. A certain number of North American cases have been reported, although most of these persons incurred their original infestation in foreign parts.[31, 32] Of recent years several cases have been reported in natives of this continent,[3, 32, 33] and the question has arisen as to their origin. The appearance of such cases has reflected an increase in the extent of infestation of native cattle[33-35] (Table I). Curiously enough, the source of human infestation does not seem to be dogs, as it is in most endemic areas.[35, 36] This has led some to think that the American reservoir may be in wild animals,[37] which would render the problem of control far more difficult than in areas such as Iceland, where the disease has all but been wiped out by intelligent control measures,[38] and New Zealand, where attempts are be-

TABLE I

INCIDENCE OF ECHINOCOCCUS INFESTATION IN CATTLE AND CALVES IN THE UNITED STATES*

YEARS	NUMBER OF CATTLE EXAMINED	NUMBER OF CATTLE WITH HYDATIDS	REFERENCE
1897 to 1899	8,831,927	6	35
1937	17,314,451	1,923	34
1941	15,520,427	3,525	34

*Figures for sheep and pigs not available for recent years, but rate of infection higher than in cattle in 1897 to 1899.[35]

The anatomy of the coronary arteries is such that the larvae are most easily carried directly into the right coronary, and, as a result, the proportion of cysts is roughly 3:2 for the right and left sides of the heart, respectively.[17, 28]

The cysts may develop in several ways. A certain proportion of them die after attaining varying sizes, after which, unless they are so placed or so large as to cause mechanical difficulties, they become fibrosed, with or without calcification, and are only discovered incidentally at operation or autopsy. Living cysts grow at what seems to be a fairly constant rate, depending on their location, and, from their size, much may be inferred regarding their age. A certain proportion of cysts rupture as a result of trauma or interference with blood supply and necrosis. When this occurs, spread of the disease frequently follows by any one of a number of routes. There may be merely local formation of multiple cysts in the tissues immediately surrounding the site of rupture, but if the rupture is into the peritoneal cavity, large blood vessels, biliary passages, or respiratory or digestive passages, distant spread will usually take place unless the cyst is dead, or unless the infesting material can be completely expelled in bile, feces, sputum, or vomitus. This infesting material may consist simply of cyst fluid and scolices, or it may contain actual "daughter cysts" formed by infoldings of germinal membrane following trauma to the cyst.[27] These daughter cysts have the capacity of independent growth when carried elsewhere in the body by the blood stream or in other ways. Table III depicts the routes of spread from rupture of primary cardiac cysts to various organs.

There are five main types of cardiac cysts, as follows: (1) dead cysts, usually markedly fibrosed or calcified, (2) living, intact cysts, (3) cysts which have ruptured into the pericardium, causing adhesions, with or without the formation of secondary cardiac cysts, (4) pedicled cysts in the heart cavities, and (5) cysts which have ruptured one or more times into the chambers of the heart.

The division of cardiac cysts into the above five groups is of importance because the clinical picture is governed by the location and viability of the cyst.

Table III

Site of Emboli From Cysts of the Heart—From Dumont[40]

Heart
(80 cases)

Brain	Kidney	Spleen	Liver
51 cases	14 cases	14 cases	1 case
(64%)	(17.5%)	(17.5%)	(1%)

and Dew[41] and Magath[33] are of the same opinion. The most telling point in Dévé's argument is that one virtually never sees primary intracranial cysts except in childhood.[43, 44] Elsewhere in the body the cysts can develop and grow asymptomatically for long periods, and are frequently not diagnosed until patients are older, whereas, in the cranial vault, such expansion cannot proceed indefinitely.

After leaving the digestive tract the larvae enter the portal circulation and are largely filtered out by the liver, where an unknown and probably variable proportion survive to form cysts. A far smaller number of larvae pass the liver filter and enter the heart and pulmonary tree, where about a third of them are retained in the capillary bed, and the remainder pass into the systemic circulation. Dévé[4] has suggested that the reason why the pulmonary filter is less effective than the hepatic is that the liver removes all of the larger larvae and that the pulmonary capillaries are relatively large. The eventual distribution of primary cysts is illustrated in Table II.

These primary cysts, contracted presumably in childhood, do not interest us further aside from the small percentage which are retained by the heart, except insofar as we are interested in differentiating them from secondary cysts arising from primary cardiac cysts. The cardiac cysts are formed by the entrance of the larvae into the coronary system.[19]

TABLE II

ROUTES OF INFESTATION AND SITE OF PRIMARY ECHINOCOCCAL CYSTS IN MAN—AFTER DÉVÉ[4]

TRANSMISSION		PRIMARY CYSTS
Intestine	→	Very rare
↓ 100%		
Liver	→	75%
↓ 25%		
Lungs	→	8.5%
↓ 16.5%		
Heart	→	0.5%
↓ 16%		
Systemic circulation		

Muscles	Spleen	Kidney	Brain	Bone	Miscellaneous
5.5%	2.5%	2.0%	1.5%	1.0%	3.5%

later die, and still others progress to give symptoms, may develop daughter cysts, and may even rupture themselves at a later date to cause further dissemination. If the particles forming emboli are quite large, they usually cause local ischemia about the infarcted area, with death of the cystic material, followed by scarring about the site of implantation.[10] The affected vessel may even recanalize after the death of the occluding cystic matter. Aside from the mechanical effects, there is no specific symptomatologic reaction to the implantation of germinal elements in the peripheral tissues.

Another important group of systemic disturbances is attributable to the reaction of the body tissues, particularly the vascular system, to the protein substances freed from the cyst at the time of rupture. The original invasion of the body by the cysts usually results in the development of sensitivity to echinococcal materials. However, as long as a cyst is intact in the body, the system is protected by the cyst membrane from exposure to such allergens. This sensitivity forms the basis for the numerous skin and serologic tests now in general use for the diagnosis of echinococcal infections.[42, 45-50] In this regard, it is of interest that patients with single cysts of the brain frequently fail to give a positive skin test, although the test may become positive after operative extirpation of such a cyst.[51]

When a cyst ruptures in the heart, freeing cyst contents in the peripheral blood stream, the reaction may be of any degree, depending on the viability of the cyst, and probably on other factors, such as duration of previous infestation, previous ruptures, and the like. As a rule, the effects of such a reaction constitute one of the principal components in the clinical picture.

A third important group of symptoms arises from the effect of the primary cysts on the function of the myocardium, either as a result of myocardial destruction, interference with valvular efficiency, or disturbance of conduction. Curiously enough, this type of disturbance does not figure prominently in the reported cases; it was noted in only thirteen of the fifty-six cases that we have reviewed.

Dévé[24] has pointed out that, in carefully followed cases, rupture of cysts into the pericardium is seldom fatal, and that rupture into the systemic circulation usually takes place several times before death occurs. Our case (Case 1) illustrates this, as do other case reports.[52-54] Were clinical data more fully described in other reported cases, this list would doubtless be longer.

Clinical Course.—Of the fifty-six cases of hydatid cysts of the left side of the heart that we have collected from the literature, fifteen, or 27 per cent, were discovered incidentally at autopsy.[10, 16, 17, 55-65] In these cases the cysts remained silent throughout life. Nine, or 16 per cent, of this group died suddenly, and an intact cyst constituted the only lesion at autopsy.[66-74] Although in this group there is some doubt as to whether or not the cyst was the cause of death, the relative fre-

The first group is one which is least frequently of clinical significance. As a rule such cysts are found only at autopsy, and do not cause symptoms except when death of the cyst is preceded by rupture, with dissemination of viable echinococcal material. They may, however, be of such size or so located as to interfere with the function or circulation of the heart.

The living, intact cysts are perhaps the most important of the entire group, for, if they are detected roentgenologically, the indication is for surgical exploration and extirpation to prevent subsequent rupture or further growth, which may interfere with cardiac function.

Pericardial involvement, with its complications, may be an indication for surgical intervention, although the potential dangers and technical difficulties of such operations may be prohibitive. Dévé[24] has pointed out that it is rupture inwards, rather than outwards, which causes most trouble from cardiac cysts.

Pedicled cysts in the chambers of the heart are found from time to time post mortem. Occasionally they cause symptoms if they are so large or so placed as to interfere with valvular function. Their detection is unlikely, although the possibility was considered ante mortem in one case.[6] Under such circumstances operative intervention might be conceivable, but differentiation from other valvular lesions would be difficult.

The detectable cysts are probably largely contained in the fifth group. Group two may be detected in routine chest roentgenograms, and since such examinations are becoming a more and more common practice, this will undoubtedly happen more frequently than in the past. However, since such cysts are frequently asymptomatic, they will not be found by other means in significant numbers. When cyst contents are poured into the systemic circulation, however, symptoms almost always result. It is at the time of rupture, therefore, that most ante-mortem diagnoses should be made. This will be most often true of cysts which pour daughter cysts into the vascular tree.

When such a cyst ruptures, several systemic disturbances are to be anticipated. The first cause of such disturbances is mechanical, that is, the result of arterial occlusion by daughter cysts and other material, e.g., cyst wall, scolices, etc. It is of interest in this regard that when such material occludes arteries and causes symptoms, it is usually a large artery that is involved, e.g., femoral, iliac, carotid, or renal. This is probably due to the fact that involvement of smaller arteries is obscured by the general systemic and vascular reactions to be noted below.

A secondary effect of these emboli is the dissemination of germinal elements from the primary cyst into the peripheral tissues and organs; these may or may not survive and later give rise to secondary cysts with or without eventual clinical significance, depending on the survival of the patient and on the survival of the secondary implantations. Many of these die shortly after implantation, others survive to form cysts which

of disturbance of cardiac function by the cysts, even in cases in which the cysts are large and the continuity of the myocardium is definitely disrupted. This is in part explained by the nature of the encapsulating membrane, which serves in lieu of myocardium where it replaces it.

If the patient recovers from the initial shock of the rupture, he may be left with a gangrenous extremity, unilateral renal shut-down, hemiplegia, or other embolic sequelae; he may be entirely asymptomatic, only to be struck down by a subsequent recurrence or by the gradual development of multiple intracranial cysts, with epilepsy or other symptoms of intracranial growth;* or again the extension may be to other peripheral organs with corresponding symptoms.

It is not entirely justifiable to conclude that a cardiac cyst exists simply because of the sudden appearance of a shower of hydatid emboli in the peripheral circulation, because such cysts may originate from the rupture of pulmonary cysts into the pulmonary veins. This, however, is an occurrence which has only rarely been reported, for pulmonary cysts usually rupture into bronchial passages.

Diagnosis, Treatment, and Prognosis.—Of the fifty-six cases we have collected from the literature, in five,[3, 7, 29, 30, 51] or possibly six,[6] the diagnosis was made prior to death. In an additional case the diagnosis was made by Dr. H. R. Dew (Case 5 of this report). The diagnosis of cardiac echinococcosis is essentially the same as it is in the case of other organs of the body, with certain added difficulties which arise from the fact that heart cysts tend to be asymptomatic, and can, therefore, usually be detected only roentgenologically. There are a number of skin and serologic tests, none of which are universally satisfactory,[42, 45-50] although high specificity is reported for several—one as high as 85 to 95 per cent.[33]

Eosinophilia is reported in a considerable proportion of cases, although it is not always present, even after rupture of a cyst. The presence of one or more cysts in peripheral organs may serve as the clue which will lead to roentgenologic detection of a cardiac cyst. The sudden occurrence of unexplained anaphylactoid collapse, particularly in persons born in regions where hydatid disease is endemic, should always arouse suspicion of rupture of a cyst, particularly in the heart, for the freeing of echinococcal protein directly into the blood stream seems to cause such reactions in a greater proportion of cases than does the rupture of cysts elsewhere.

There is reason to believe on theoretical grounds that the presence of a cyst or cysts in the myocardium should give rise to abnormalities in the electrocardiogram, and a recent case in which tracings were obtained[3] bears this out. In our case (Case 1), the electrocardiogram was entirely normal except for minimal depression of the S-T segment in Lead IV.

*In this regard, Dévé's experimental production of intracranial pressure symptoms by the injection of scolices was probably the earliest and most satisfactory method for the study of increased intracranial pressure in the intact animal.[23]

quency of its occurrence suggests the sudden appearance of a fatal arrhythmia. Thirteen, or 23 per cent, had signs and symptoms of impaired cardiac function.[3, 6, 7, 14, 18, 29, 30, 68, 69, 71, 75-77]

In another group of cases the course was one of rupture of the cardiac cyst, with more or less prompt fatality, either due to anaphylaxis or to circulatory obstruction by cyst contents in the heart itself or in major peripheral vessels. In fourteen (25 per cent) of the fifty-six cases, rupture was the primary cause of death. Rupture, however, need not necessarily be followed by death. Our case (Case 1) is an example of repeated rupture into the heart, and, in sixteen (27 per cent) of the fifty-six cases, rupture had occurred previously without causing death. Without having ever seen a case, and at a time when adequate case reports were not yet available, Dévé wrote a prophetic description of what the clinical picture of rupture of a cardiac cyst into the systemic circulation would be, and subsequent observers of such cases have confirmed rather than corrected his predictions. His remarkable description follows (our translation); it is taken from a quotation by his pupil, Mlle. Dumont,[40] in her thesis on cardiac echinococcosis, written in 1918.

"Sudden onset in apparently totally healthy subject. Immediate onset of anxiety with or without lipothymic state or epileptiform crisis, or merely a sensation of tingling throughout the extremities. Headache with or without ocular disturbances. Often vomiting. Soon, pain in the extremities, accompanied by weakness or mild spasticity, accompanied particularly by circulatory disturbances of the extremities giving rise sometimes to ecchymotic areas or to marbling, sometimes to a true Raynaud's syndrome: cyanosis of the extremities, cold, decrease in intensity or disappearance of arterial pulsations, pain. Without doubt, one will often find, in such cases, a more or less profuse albuminuria, with or without hematuria, caused by microscopic renal emboli. Finally one can predict that an urticarial eruption may ensue to clarify the nature of these disturbances.

". . . such a description is entirely theoretical. Thus it makes no pretentions other than to state the problem and to call the attention of clinicians to a matter which has up to now remained obscure and which appears to us interesting. There is no doubt that, sooner or later, new clinical observations will fill the gaps (in our knowledge) and permit the substitution of a real symptomatology for our hypothetical estimate."

It is a real tribute to Professor Dévé that "substitution" of the "real symptomatology" is not necessary.

The patient's course subsequent to rupture of a cyst may take almost any form, depending upon the severity of the reaction to the echinococcal proteins, on the size and type of cyst ruptured, on the site and extent of embolic involvement, and on the degree of impairment of cardiac function resulting from interference with myocardial integrity. One of the most remarkable features of cardiac hydatids is the relative rarity

DISCUSSION

Echinococcal infestation of American cattle seems to be increasing, according to reports of slaughterhouse inspectors (Table I), and there is no reason to feel that the same is not true among our sheep and hogs, although figures are not available. This increase may well be reflected sooner or later by the appearance of cases of echinococcal infestation acquired in this country, although in the past almost all cases have been in foreign-born persons.[31, 32] Large numbers of American physicians are active at this time in areas where the disease is endemic (North Africa, Europe, Australia, and New Zealand), and there is every likelihood that they will encounter local inhabitants with this disease. Our own troops are not likely to become infested with echinococcus, however, because it is a disease which seems to be contracted predominantly in childhood. Transportation advances in the near future should bring physicians throughout the world into contact with a larger number of transient or permanent visitors from areas where this disease is common. Thus our physicians are more likely than before to be faced with the problems of echinococcosis.

Aside from the fact that such cases may be more frequently seen in the near future in North America, it is quite possible that advances in the technique of thoracic and cardiac surgery will offer cure, or at least relief, from a condition which previously had been of clinical interest but without therapeutic potentialities. Cardiac echinococcosis can profitably be added to the list of diseases of the heart which are amenable to surgical treatment.

SUMMARY AND CONCLUSIONS

Fifty-six cases of echinococcus infestation of the left side of the heart have been collected from the literature, and five new cases added. Invasion of the left side of the heart by echinococcus cysts has been discussed in detail from the point of view of pathogenesis, clinical course, diagnosis, prognosis, and treatment. Although this is a rare disorder, it is worthy of emphasis in that it represents a type of unusual heart disease for which surgical relief is promising, now that improved techniques of thoracic exploration have been developed.

REPORT OF CASES

Case 1 (M59783).—M. D., a 43-year-old Italian housewife, was first seen at the Peter Bent Brigham Hospital on March 12, 1941, because of attacks of unconsciousness of nine years' duration. The family and past history were noncontributory except that she was born in Italy and came to this country in 1931. She had always been well until 1932, when she developed her first seizure. Her second attack occurred in 1937. Both attacks were similar, in that she was seized with sudden, sharp epigastric pain and loss of consciousness without aura. She became cyanotic, frothed at the mouth, and was found to be in profound shock; neither the blood pressure nor the pulse was obtainable. There were no

Calcification of cyst walls, as seen roentgenologically, would appear to be a confirmatory, although not a specific, diagnostic point, for it is unusual for pulmonary cysts to show calcification.[3]

Treatment of cardiac cysts is a virtually virgin field. Long[30] reports a case in which operative removal of cyst contents in a 42-year-old woman was followed by recovery. Such treatment had been suggested in the past, but so far as we know this is the first case in which such treatment has been attempted. Recent advances in technique have rendered operations on the heart and pericardium far less uncommon than previously, and it may well be that operative removal prior to rupture will be the prophylactic therapy of choice in the near future. No other effective therapy is known, unless the physician in charge has sufficient temerity to attempt injection of the cysts after puncture and evacuation of the contents, which is unlikely with cardiac cysts. The one reported attempt[29] resulted in death. Aside from the one case noted, no attempts have apparently been made to treat such cysts up to the beginning of 1943. The evaluation of surgical measures, therefore, remains to be made in the future.

In deciding on operative treatment of cardiac cysts, two important factors should be given consideration. First, it should be ascertained whether or not the cyst has previously ruptured and caused extension, for the patient may benefit little from removal of a cardiac cyst if he is already being affected by secondary intracranial cysts. Secondary cysts elsewhere than in the brain can be dealt with later, but therapeutic success in dealing with multiple brain cysts is rare.[43] Second, one should attempt to differentiate cardiac cysts from pulmonary cysts adjacent to the heart, for the operative technique and prognosis are not identical (Case 6). Treatment should offer more if operation is undertaken prior to impairment of cardiac function by growth or intrapericardial rupture of the cyst.

It is well to point out the importance of accurate diagnosis with regard to intracranial cysts. Dew[43] has shown, as have others, that success in operative therapy of such cysts is dependent on elimination of cases of secondary involvement. Once a single primary cyst has been removed, recovery usually ensues if the patient survives the operation, but multiple secondary cysts can seldom be completely removed. A careful search for cardiac cysts, therefore, should always precede craniotomy in cases in which intracranial echinococcus cysts are suspected.

The prognosis of cysts of the heart should probably be considered unfavorable, although it is true that fifteen out of a total of fifty-six cardiac cysts were found incidentally at autopsy. Viable cysts must be expected to progress to the point of rupture or interference with cardiac function, and after the occurrence of either of the above the outlook must be considered ultimately fatal, although the patient may survive for a varying period. This may well be changed by operative treatment.

Neurologic examination revealed the following: The head was held to the left; the eyes were held in left conjugate deviation, with roving movements; the right pupil was larger than the left; there was questionable blurring of both nasal disc margins; a patch of exudate was seen in the left fundus, and one of the small arterioles was occluded; the jaws could not be opened. The arm reflexes were hyperactive, and rigidity was marked, especially on the left; the abdominal reflexes were not obtained; the leg reflexes were hyperactive, particularly on the left; Babinski, Oppenheim, and Gordon signs were present bilaterally; bilateral ankle clonus was noted, as well as fine muscular twitchings and urinary incontinence.

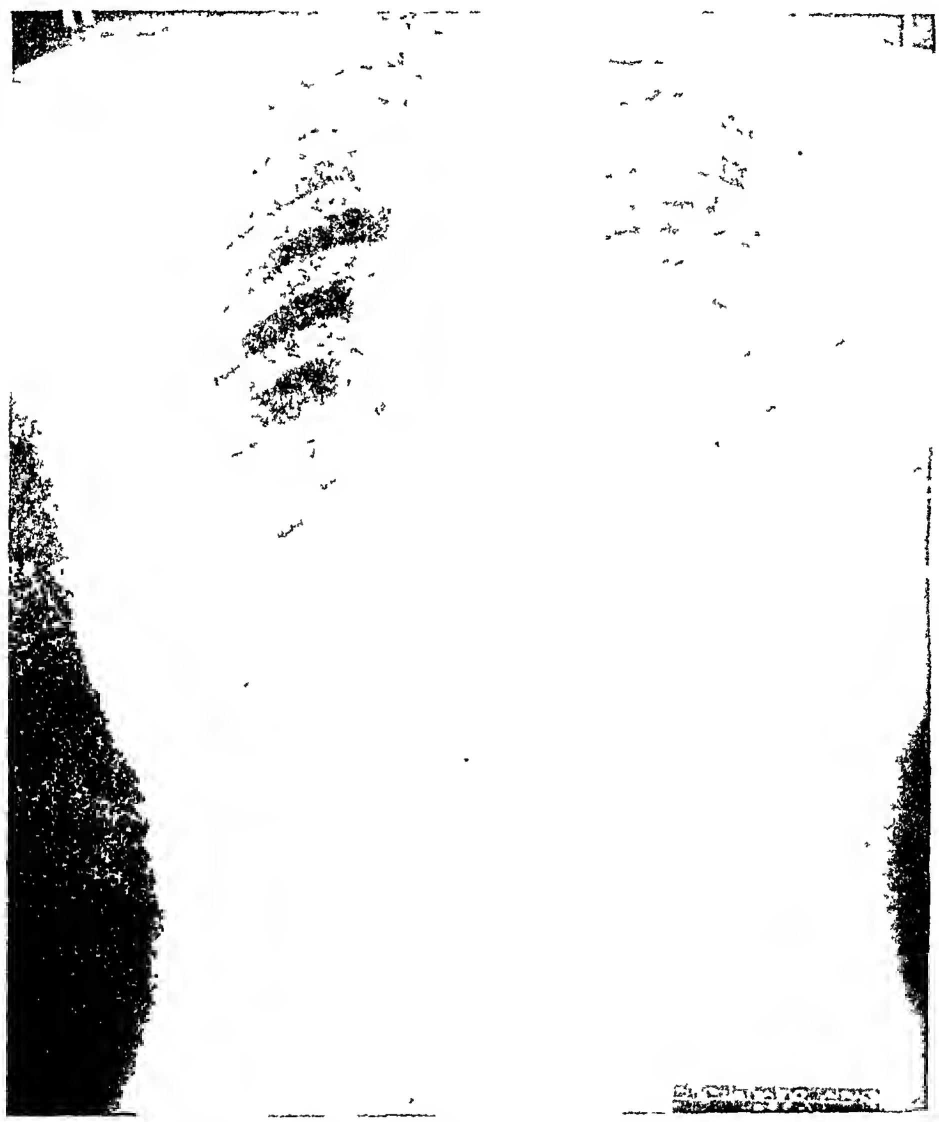

Fig. 1.—Roentgenogram of chest of patient M. D. (Case 1), showing a mass in the region of the hilum of the right lung, and another along the left border of the heart. See Fig. 2 for autopsy correlation.

On the day of admission, a roentgenogram of the chest revealed "considerable widening of the upper mediastinum and a small nodule at the auriculo-ventricular junction on the left. Lungs were clear." This roentgenogram was the same as the one taken in May, which is shown

convulsions. She was incontinent of urine, and passed foul flatus which was colored by brick-red blood. No skin lesions were noted. With symptomatic treatment patient regained consciousness within a few hours and attained complete recovery within a week. A roentgenogram of the chest in 1937 showed no abnormality of the heart or lungs except for some thickening of the pleura at the right base laterally. Roentgenologically, the stomach, duodenum, and colon were likewise normal. The patient was asymptomatic for three years.

She developed seizures in April, 1940, February, 1941, and March, 1941. These attacks were preceded by sticking and "pinching" paresthesias of the lower half of the body, especially on the left, and by flashes of light. Flaccid unconsciousness, without convulsions, ensued, and lasted about thirty minutes. During the last attack the jaws were tightly clamped together and she drooled sputum. Black spots were said to have appeared on her left arm. During the period of recovery she had difficulty in swallowing and talking and weakness of the left arm and leg. At no time were cardiac symptoms apparent. A roentgenogram of the skull showed nothing abnormal. The blood sugar was 86 mg. per cent. The spinal fluid was entirely normal. An electroencephalogram was reported as "not typically epileptic, but abnormal."

On May 23, 1941, she had two mild attacks and was readmitted to the hospital because she was suspected of having a brain tumor. A roentgenogram of the chest at this time revealed two nodular masses, one opposite the ascending aorta on the right, and the other at the auriculoventricular junction on the left; they measured 4.5 cm. and 2.5 cm., respectively (Fig. 1). These masses could not be separated from the cardiovascular shadow and did not seem under the fluoroscope to have intrinsic pulsation. The mass on the left was described as apparently having the usual auriculoventricular junction motion. A ventriculogram on June 6, 1941, revealed moderate dilatation of both lateral ventricles and the third ventricle. More than the usual amount of air was around the Islands of Reil. The ventricles were displaced slightly to the right of the midline. The patient was discharged without a definite diagnosis.

She was readmitted Dec. 16, 1942, in coma. She had been well since discharge until the evening before admission, when at suppertime she suddenly felt ill. She lay down and was swept by the familiar sensation of pins and needles which were worse on the left side. She could hardly move that arm. Epigastric and lower abdominal pain and urinary incontinence ensued, but there was no loss of consciousness, aphasia, or convulsions. Her doctor found a temperature of 97° F., a pulse rate of 80, and a systolic pressure of 70 mm. Hg. She vomited on several occasions. Several hours later her face became swollen. Thick, tenacious material came from the mouth. She began to shake as if having a chill, and soon became unconscious. The next day her physician found her in coma and sent her to the Peter Bent Brigham Hospital.

Physical examination revealed a well-nourished patient in coma and breathing irregularly. Facial edema was noticeable. Many petechiae were observed over the chest, back, arms, and conjunctivae. The lips were dry. Rhonchi were heard throughout both lungs, and moist râles were heard at both bases. The heart sounds and rhythm were normal. The blood pressure was 84/66. Neither the brachial nor common carotid pulse could be felt on the right. The right arm was cooler than the left, but both legs were of the same temperature. Neither dorsalis pedis artery could be felt.

was partly filled with blood clot and partly with gelatinous and membranous material. Its fibrous capsule had replaced the atrial myocardium. Just above the auriculoventricular junction, next to the aortic valve, there was a 1.5 cm. point of rupture.

The entire right hemisphere of the brain was somewhat atrophic, and the right temporal and occipital lobes showed areas of degeneration, but no cysts were found. Several small translucent cysts were present in the spleen.

Fig. 3.—Heart of patient M. D. (Case 1), showing the echinococcus cyst, full of blood clot, lying in the wall of the left atrium. The marker indicates the point of its rupture into the atrial cavity.

An old small echinococcus cyst was present in one kidney, and one of minute size was seen microscopically in the thyroid. No cysts were found in the lungs, liver, alimentary tract, pancreas, gall bladder, or pelvic organs.

Emboli and thrombi consisting of membranes and cyst contents were present in the left ventricle, both internal carotid arteries at their junction with the circle of Willis, the left middle cerebral artery, the celiac axis, the superior mesenteric artery, the right renal artery, and the splenic artery.

in Fig. 1. The electrocardiogram was entirely normal except for minimal depression of the S-T segment in Lead IV. The urine contained a few leucocytes and many granular casts. The hemoglobin was 14.5 Gm. The leucocyte count was 17,500, with 96 per cent polymorphonuclears, 4 lymphocytes, and no monocytes or eosinophiles. The blood urea nitrogen was 19 mg. per cent. The spinal fluid on admission contained 300 erythrocytes and 34 mg. per cent of protein. Just before death it was opalescent and faintly reddish, and contained 30,000 erythrocytes and 53 mg. per cent of protein. Despite therapy the patient lapsed further into coma and died on December 18, two days after admission.

Autopsy.—Autopsy revealed numerous petechiae over the thorax, buccal mucosa, and conjunctivae. The heart was grossly somewhat enlarged. The right auricle and ventricle were normal. Four cysts were present on the left side of the heart (Fig. 2). On the posterior surface there was an intact cyst 3.5 cm. long and 1.5 cm. in the anteroposterior diameter overlying the interventricular septum and left ventricle. Between the ascending aorta and superior vena cava there was a tense ovoid

Fig. 2.—Heart and lungs of patient M. D. (Case 1), showing the paracardiac cyst at *A* and the cardiac cyst at *B*.

cystic mass 4 cm. long, 3.5 cm. in transverse diameter, and 3 cm. in the anteroposterior diameter (cyst *A* in Fig. 2). It was located outside the heart, but had destroyed by pressure all but a 4 mm. thickness of myocardium between the cyst and the cardiac lumen. No erosion had occurred into the aorta or vena cava. The third cyst was 2.4 cm. in diameter and was located on the left margin of the heart at the auriculoventricular junction. It protruded from the epicardial surface and was covered with densely adherent pericardium (cyst *B* in Fig. 2). The fourth cyst was roughly spherical, measuring 3.5 cm. in diameter, and was located on the posterolateral aspect of the left atrium (Fig. 3). It

On examination he appeared to be a very healthy and well-developed young man. The pulse rate was 74, the blood pressure, 124/88, and the temperature, normal. His chest showed a slight increase in size on the left; the apex beat was in the fifth intercostal space, 4½ inches from the midline. An area of dullness continuous with the cardiac dullness extended out to the scapular line and up as far as the third rib. The vocal resonance and vocal fremitus were diminished over this area, but were present below towards the left base posteriorly. The heart sounds were normal, and an electrocardiogram, taken later, showed no abnormality.

Fig. 4.—Roentgenogram of the chest in Case 6, showing the rounded tumor mass which at operation was found to be a parapericardial hydatid cyst of the left lung. The small lead shot was used as a marker.

Nothing abnormal was detected in the other organs. Roentgenograms revealed an oval shadow which was continuous with the cardiac shadow above and to the left (Fig. 4). The diagnosis of hydatid cyst in close contact with the heart was made. The Casoni intradermal test was positive.

Operation, on Feb. 8, 1940, was performed under gas and oxygen anesthesia. Thoracotomy, with removal of 3 inches of the seventh rib

Comment.—This is an excellent illustration of involvement of the left side of the heart, with widespread embolic dissemination. The clinical picture of anaphylactic shock with embolic manifestations is classical for this condition.

Cases 2, 3, and 4 were collected from the Hydatid Registry of the Royal Australasian College of Surgeons by Dr. Louis E. Barnett, of New Zealand, who has kindly allowed us to publish their abstracts. Although data concerning these cases are few, they are being included as illustrations.

CASE 2.—"Australian: Operated on for ruptured liver cyst in August, 1933, and said to have multiple metastatic cysts elsewhere due to a leaking primary liver cyst. Details very meagre and inconclusive."

Comment.—This was apparently one of those cases in which cardiac involvement was not significant. It is unusual in that both liver and heart were involved simultaneously.

CASE 3.—"New Zealand: Little girl age 5; unsuccessful operation on December 7, 1938, for cerebral cyst. Postmortem examination revealed cyst in the left ventricle of the heart and also 2 cysts in the liver."

Comment.—This is another case in which liver and heart were simultaneously involved, and in which the cardiac cyst was discovered incidentally at autopsy.

CASE 4.—"New Zealand: Lad age 18 who died suddenly from the effects of rupture of a degenerated cyst into the left ventricle. Autopsy revealed embolic plugging of the aorta from the level of the first lumbar vertebra to the common iliac artery with hydatid material."

Comment.—This case illustrates sudden death from rupture of a cyst and massive embolic manifestations.

CASE 5.—Dr. Harold R. Dew, Professor of Surgery, University of Sydney, Australia, recently wrote us as follows concerning a case of hydatid cyst. "I saw a boy the other day with an undoubted cardiac cyst, although there is no sign of it clinically or radiographically, but he had an embolism of hydatid membrane in the femoral artery following a typical anaphylactic attack. The hydatid membrane was removed from the lumen of his artery, but his leg became gangrenous and he had to have an amputation. He will, of course, be followed up later."

Comment.—This is an illustration of one of the not uncommon ways in which a cardiac cyst makes itself known, as Dr. Dew has pointed out. It is important to recognize the possibility, however, that rupture of a pulmonary cyst into a pulmonary vein may give the same picture, as is illustrated by the following case.

CASE 6.—A young farmer, E. T., aged 22 years, was admitted to the hospital on Jan. 30, 1940, on the service of Dr. Harold R. Dew, with a story of attacks of unexplained pleurisy over the preceding two years, with some discomfort in the left side of the chest and occasional attacks of palpitation on exertion. He had had a roentgenogram in the country, and the diagnosis of cardiac hydatid cyst had been made.

paresis, with left homonymous hemianopsia. In addition, he had a convulsive state which started on the left side and later became generalized. Mentally he showed retention defects, with defective recent memory. His main difficulty was his paranoid state. No direct evidence of cardiac or pulmonary involvement with cysts has yet been obtained.

Comment.—Multiple echinococcus cysts of the occipital lobe were found in this patient at operation. He has since developed paranoid tendencies. Dumont[40] and Dew[43] feel that such cases are almost certainly secondary to cardiac involvement, but ultimate decision must await the development of changes in the roentgenograms or post-mortem examination to ascertain whether the source was lungs or heart.

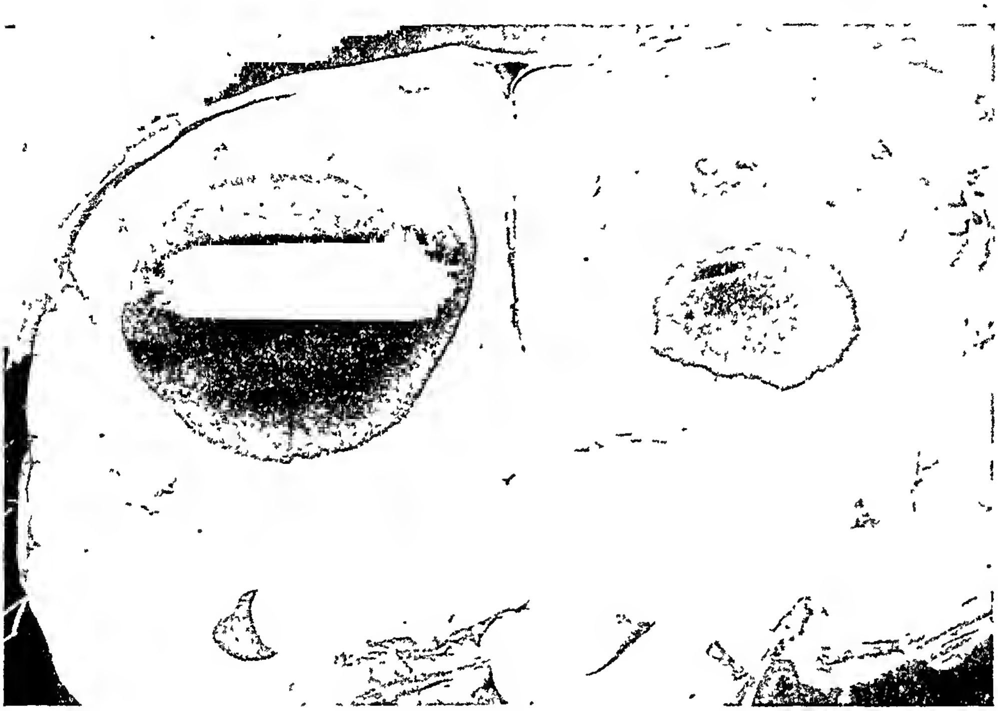

Fig. 5.—Cross section of brain of patient L. C. (Case 8), showing the two large cerebral echinococcus cysts.

CASE 8 (S636).—L. C., a 24-year-old, Italian-born laborer, was admitted to the Peter Bent Brigham Hospital Nov. 29, 1913, with a history of diffuse headache and gradual loss of use of the right arm for two months, and numbness and weakness of the right leg for one month. These symptoms had gradually increased in severity, making walking difficult. For one week before admission, he had a speech defect. The family history and past history were noncontributory except that the patient had had malaria one year previously.

On physical examination the patient had right homonymous hemianopsia. The optic discs were slightly choked. The right pupil was larger than the left. Partial motor aphasia was present. The heart was entirely normal in size and shape; the sounds were normal, of good quality, and without murmurs. There were slight dullness and bronchovesicular breathing at both apices, more pronounced on the right than on the left. The liver was not enlarged. The edge of the spleen was just palpable. The left arm was normal. The right arm was paralyzed with-

in the midaxillary line, was undertaken. The pleura was found adherent (suspected because of the previous pleuritic attacks), the cyst was evacuated (about 2½ pints of fluid were obtained), the laminated membrane was removed, the cavity was swabbed out, and a drainage tube was inserted; the skin incision was loosely closed. During the operation the wall of the left ventricle was felt through the pericardium, which made up part of the adventitia of the cyst.

During the first few days after operation the patient had some interesting attacks of tachycardia and cardiac distress which I believe were due to sudden dislocation of the heart towards the large cavity to the left. These subsided after a few days. He had a mild, passive, pleural effusion which cleared up without any treatment in about ten days. He was discharged March 10, 1940. Roentgenograms now showed that the left hemithorax was normal.

Comment.—This patient had a parapericardial cyst of the left lung; the case is included as an illustration of the diagnostic difficulties encountered in differentitating cardiac from extracardiac cysts.

Cases 7 and 8 are from the files of the Peter Bent Brigham Hospital. Although both have been reported previously,[51, 78, 79] Case 7 was not suspected at the time as being one of cardiac cyst, and Case 8 seems appropriate for emphasizing the typical features of rupture of a cardiac cyst. In these reports there was no mention of cardiac cysts.

CASE 7 (S28014).—M. G., a 41-year-old Italian photographer, was referred to the Peter Bent Brigham Hospital on Jan. 18, 1927, with a diagnosis of brain tumor. His illness began with the insidious onset of headache over a period of two years, followed by failure of vision in the right eye and slight loss of memory.

Physical examination revealed weakness on the left side, left homonymous hemianopsia, and bilateral choked disks of 2½ diopters. Neurologic examination was otherwise negative. The heart sounds were regular and of good quality.

A stereoscopic roentgenogram of the chest revealed a small area of infiltration at the apex on the left, largely fibrosed and partly calcified. The lungs elsewhere were normal. The mediastinal and cardiac contours were not remarkable. Ventriculograms revealed dilatation of both lateral ventricles and displacement of the third ventricle to the left, suggesting a tumor of the right occipital lobe. Operation was delayed for several days, and the patient suddenly became restless and vomited on several occasions. He had an attack of unconsciousness lasting about one minute. The following day he had a severe headache and was restless. A few hours later he became drowsy, and by afternoon was unconscious; he was ashen, and his respiratory rate was 8 per minute, with long periods of apnea. He was immediately given 75 c.c. of 15 per cent sodium chloride solution intravenously, and improved. A right subtemporal decompression was performed that evening, and ten days later hydatid cysts were removed from the right occipital lobe. After a somewhat stormy convalescence, recovery was excellent for a period of several years. In 1931, however, he began to have epileptic attacks, usually after a bout of drinking. In 1938 he had to be institutionalized because of the development of paranoid tendencies. When last examined by Dr. Louise Eisenhardt, in July, 1942, he had a mild left-sided hemi-

9 cells per cubic millimeter; tests for globulin and the Wassermann reaction were negative. An echinococcus complement fixation test on the patient's serum postoperatively was reported as positive.

The patient shortly became drowsy, restless, and finally stuporous, and developed complete motor aphasia. On Dec. 4, 1913, Dr. Cushing removed three echinococcus cysts, the size of golf balls, from the left temporal region.

After the operation the patient was temporarily improved, but soon developed signs of an increase in intracranial pressure. The bone flap was eventually removed, and many aspirations of bloody yellow fluid were performed subsequently. Re-exploration was done March 3, 1914, but no other cyst was found. After each aspiration the patient was better, and at times was able to walk and use his right arm to some extent. As signs of an increase in intracranial pressure returned he would become worse. Five and one-half months after admission to the hospital, in May, he began to grow worse rapidly, with loss of appetite and emaciation. In June he became stuporous, and died on June 14.

Fig. 7.—Heart of patient L. C. (Case 8), showing the cystic mass (ruptured post mortem) lying in the cavity of the left auricle.

Autopsy revealed echinococcus cysts in the brain and heart, but not in the liver, lungs, or any other organ. In the brain there was a cyst

out atrophy. Although the legs were normal with respect to strength and sensation, some ataxia was noted bilaterally with the heel to knee test. The arm reflexes on the left were not obtained; those on the right were hyperactive. The knee jerks were bilaterally hyperactive. The Babinski, Oppenheim, and Gordon tests were negative; the Romberg test was positive.

Fig. 6.—Heart of patient L. C. (Case 8), showing large mass attached to the superior portion of the right auricle.

A roentgenogram of the skull showed nothing abnormal. The blood Wassermann reaction was negative. Urine analysis was negative. The leucocyte count was 7,500, with 74 per cent neutrophiles and 7 per cent eosinophiles. The spinal fluid was under normal pressure; there were

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8 cm. in diameter in the right occipital region, and another 3½ cm. in diameter in the left midhemisphere, extending posteriorly to the occipital lobe (Fig. 5). The heart weighed 410 grams with its cyst attached. Attached to the superior portion of the right auricle and running posteriorly to the level of the inferior region of the heart, was a large mass covering the base of the heart (Fig. 6). The mass was fluctuant and was approximately 8 cm. in diameter. It was slightly lobulated. It had no connection with the vessels or the chambers of the heart, but was closely connected to the walls of the auricle. In the left auricle a mass about 3 cm. in diameter was found to be adherent to the auricular septum, hanging from its superior pole down into the auricle, making a mass possibly one-third as large as the capacity of the chamber itself. The wall of this cyst chamber was about 1 mm. in thickness; it was white and rather friable. In removing the heart it was apparently ruptured (Fig. 7). Hooklets were demonstrable in the cyst contents from both brain and cardiac cysts. No scolices were seen.

Comment.—This is another case which illustrates cerebral cysts secondary to primary cysts of the heart; the existence of the cardiac cyst was unsuspected at the time of the brain operation. The cyst in the left auricle was of the pedicle type, but had given rise to no cardiac signs or symptoms.

The authors wish to acknowledge their sincere gratitude to Professor H. R. Dew, of Sydney, Australia, and Sir Louis Barnett, of New Zealand, for the use of cases and advice; to Drs. José Arce, Pedro Cossio, and José M. Jorge, of Argentina, for advice and materials; and to Dr. A. W. Miller, of the Department of Agriculture, for statistics on echinococcosis in the United States.

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HEART DISEASE IN THE SOUTH

I. A Statistical Study of 1,045 Cardiac Deaths

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SEVERAL interesting studies of the incidence and etiological types of heart disease, based on clinical material from every section of the United States, have been published.[1-11, 19] Relatively few of these surveys[3, 5, 6, 9, 15] originated in the South, and fewer[19] considered autopsy material. One general impression gained from these reviews was that rheumatic heart disease is relatively insignificant in the South. The surprising number of patients with rheumatic heart lesions encountered on the wards and in the clinics of the Charity Hospital of Louisiana at New Orleans instigated this study. This was later expanded to a statistical study of cardiac deaths at this institution. The autopsy records of the years 1935 to 1940, inclusive, were reviewed, and all deaths due primarily to heart disease were studied* and classified etiologically according to the criteria of Classification of Heart Disease of the American Heart Association. The diagnoses were made on autopsy data, and, in cases of heart disease which does not cause characteristic anatomic abnormalities, on clinical observations. In those cases in which two or more etiological types of heart disease were present, the one which was the cause of death determined the classification under which it was included, and the coexisting types were listed as associated conditions. In a few cases this was impossible, and these were listed as a combined group. Since this survey was confined to charity cases, it covered heart disease in the lower economic groups only.

A total of 8,313 autopsies were performed during this period. In this series, 1,045 deaths (12.6 per cent) were attributed primarily to heart disease. The majority of these persons (665, or 63.6 per cent) were Negroes and the remainder (380, or 37.4 per cent) were white. The age at death varied from stillborn to 98 years. There were 704 males (67 per cent) and 341 females (33 per cent). Figs. 1 and 2 show the causes of cardiac deaths and the incidence of each in the white and Negro races.

Hypertensive.—The greatest number of cardiac deaths were due to hypertensive heart disease. Four hundred twenty-three persons (40.5 per cent of the entire series) died of this condition, of whom 294

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Received for publication April 15, 1944.

*The members of the Pathology Department of the Hospital and of the Louisiana State University School of Medicine were very cooperative, and assisted in the study of records which proved difficult to interpret.

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(69.5 per cent) were Negroes and 129 (30.5 per cent) were white. Of the Negro persons, 185 (63 per cent) were males. The percentage of males was also higher in the white race, namely, 70.6 per cent, or 101 cases. The distribution according to age is clearly shown in Fig. 3. The most commonly associated cardiac complication in this group was arteriosclerosis, which occurred in 143 cases (33.6 per cent). Rheumatic heart disease was present in 17 (4 per cent), and syphilitic heart disease in 8 (1.8 per cent).

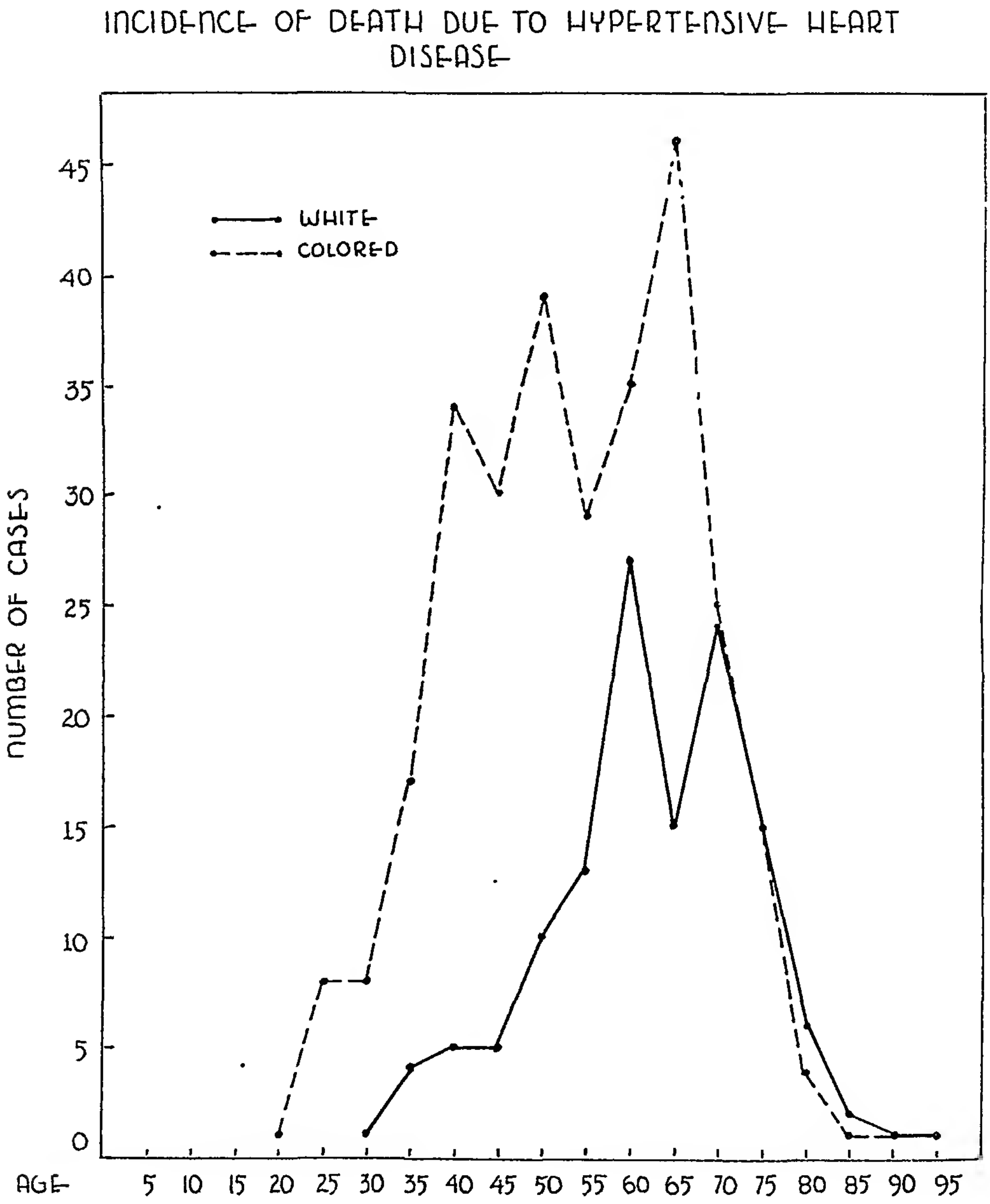

Fig. 3.

Arteriosclerotic.—Two hundred seventeen deaths (20.7 per cent) were due primarily to cardiac arteriosclerosis. The incidence in the white race was 129 (59.4 per cent), as compared to 88 (40.6 per cent)

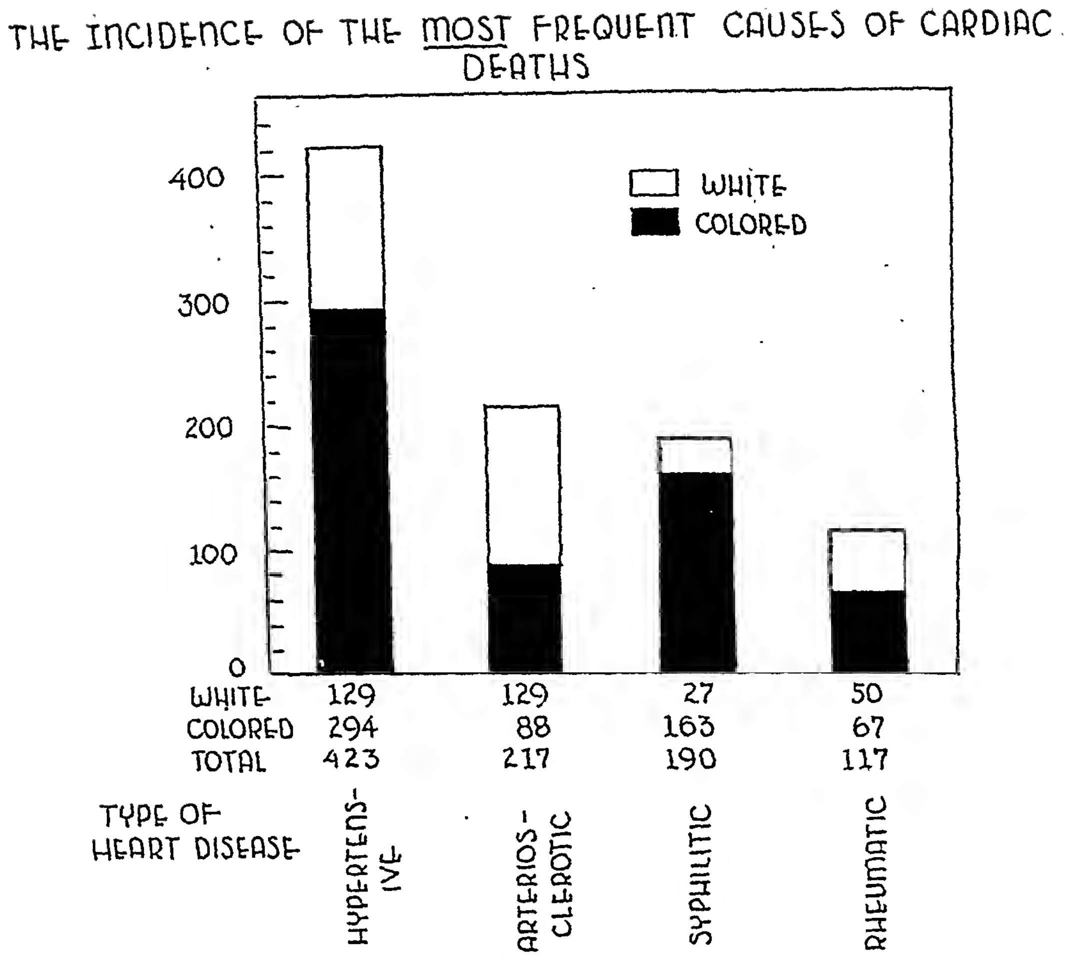
THE INCIDENCE OF THE MOST FREQUENT CAUSES OF CARDIAC DEATHS
400
300
200
100
0
WHITE
COLORED
WHITE 129 129 27 50
COLORED 294 88 163 67
TOTAL 423 217 190 117
TYPE OF HEART DISEASE
HYPERTENS-IVE
ARTERIOS-CLEROTIC
SYPHILITIC
RHEUMATIC

Fig. 1.

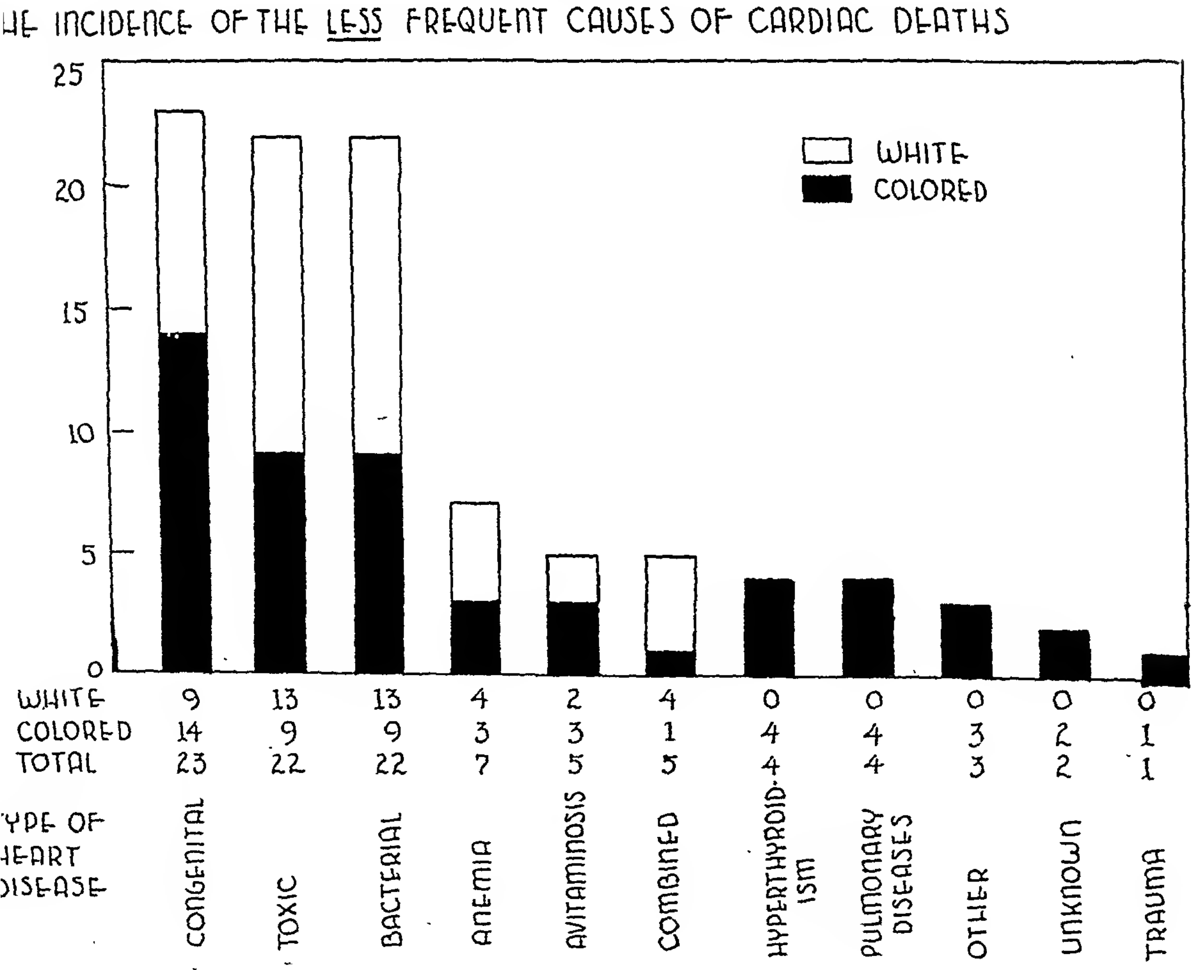
HE INCIDENCE OF THE LESS FREQUENT CAUSES OF CARDIAC DEATHS
25
20
15
10
5
0
WHITE
COLORED
WHITE 9 13 13 4 2 4 0 0 0 0 0
COLORED 14 9 9 3 3 1 4 4 3 2 1
TOTAL 23 22 22 7 5 5 4 4 3 2 1
YPE OF HEART DISEASE
CONGENITAL
TOXIC
BACTERIAL
ANEMIA
AVITAMINOSIS
COMBINED
HYPERTHYROID-ISM
PULMONARY DISEASES
OTHER
UNKNOWN
TRAUMA

Fig. 2.

were subacute bacterial vegetations on the rheumatic lesions; arteriosclerosis, 13 cases; bacterial endocarditis of the involved aortic valve, 6 cases, in 3 of which the lesions were acute, and, in the other 3, subacute; and hypertension, 5 cases.

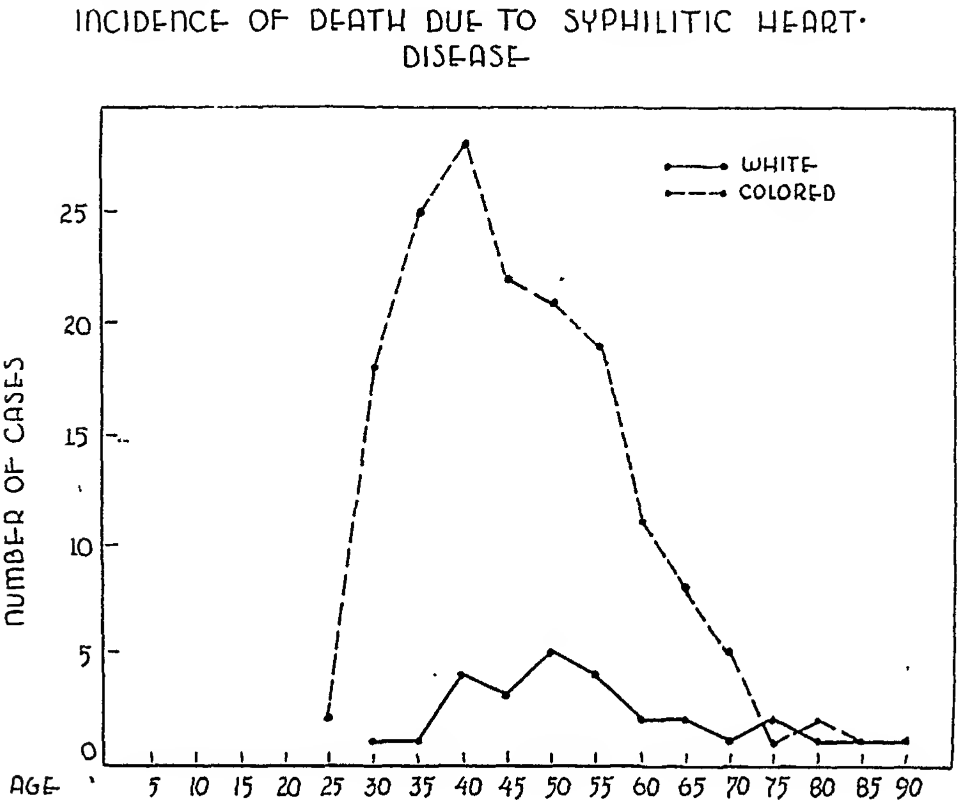

Fig. 5.

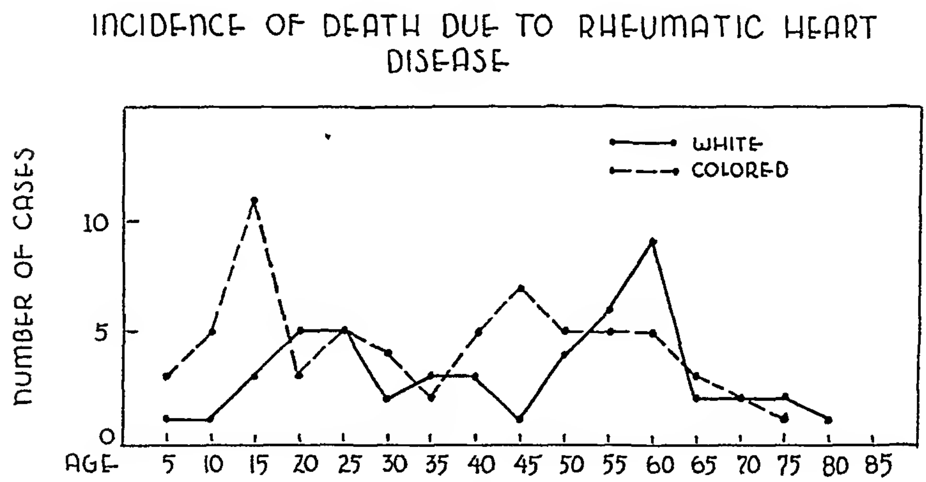

Fig. 6.

Rheumatic.—The percentage of deaths due to rheumatic heart disease was 11.1 per cent, or 117 of the entire series; 67, or 57.3 per cent, of these persons were of the Negro race. As shown in Fig. 6, there

in the Negro race (Fig. 4). This group included 117 cases (53.9 per cent) in which there was pathologic evidence of coronary occlusion, myocardial infarction, or both. The percentage of occlusion and/or infarction in the males with arteriosclerotic heart disease was 57.3 per cent (white), as compared to 49.9 per cent (Negro); in the females it was 54.5 per cent (white) and 51.5 per cent (Negro). Eleven, or 5.1 per cent, of the patients with arteriosclerotic heart disease died of dissecting aneurysm (only two of these were females).[17] Complicating cardiac conditions included hypertension, 47 cases (21.6 per cent), rheumatic heart disease, 10 cases, and syphilitic heart disease, 3 cases.

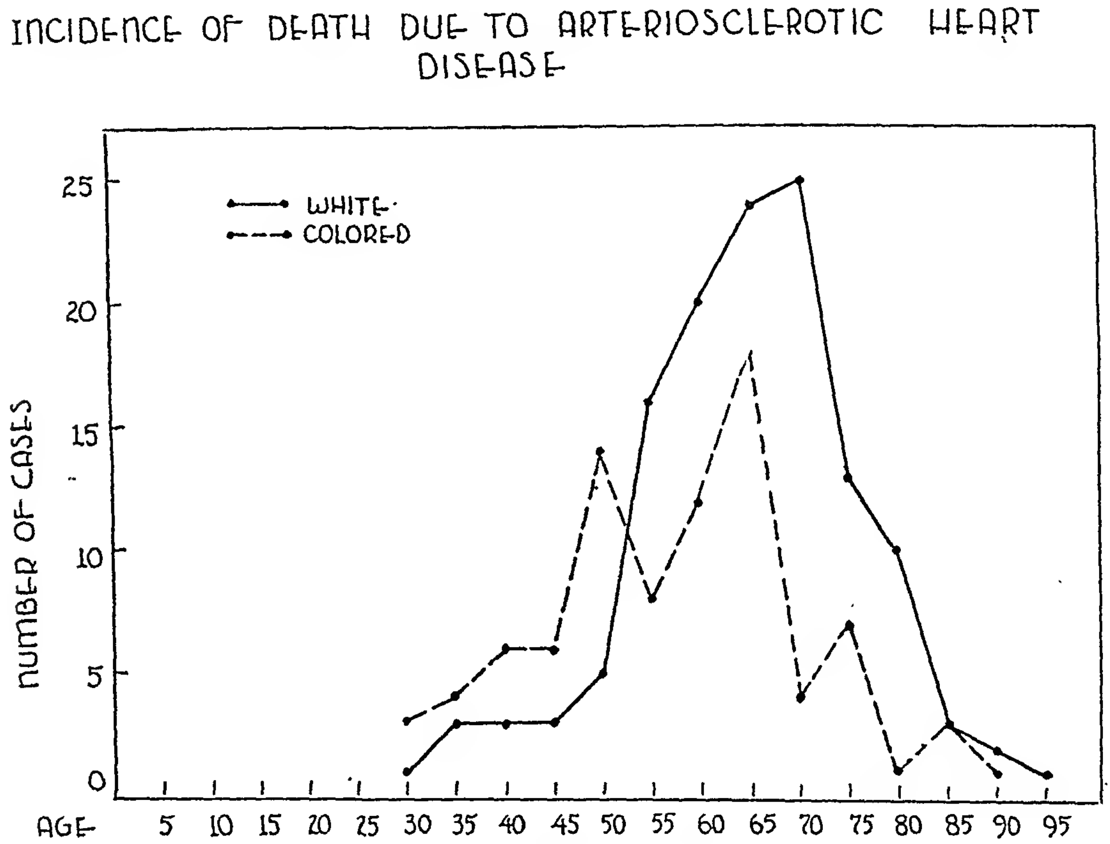

Fig. 4.

Syphilitic Cardiovascular Disease.—One hundred ninety (18.2 per cent) of the cardiac deaths were found to be due to syphilitic cardiovascular disease. The Negro race predominated, with 163 cases (86 per cent) (Fig. 5). The incidence of sex and race in this disease is of particular interest. There were 125 (66 per cent) Negro males, 38 (20 per cent) Negro females, 23 (12 per cent) white males, and 4 (2 per cent) white females. Included in this group are 77 cases in which death was due to syphilitic aortic aneurysm. It is interesting that the remaining 103 cases constitute a group in which the primary cause of death was syphilitic involvement of the heart; these comprise 10.8 per cent of the total number of cardiac deaths.

Complicating cardiac conditions in the entire syphilitic cardiovascular group included rheumatic heart lesions, 14 cases, in one of which there

Ta

INCIDENCE OF THE FOUR MOST IMPORTANT ETIOLOGI

AUTHOR	Holoubek			Laws[9]		Schwab and Schulze[5]	Stone and Vanzant[3]	Musser[15]	Maher et al.[13]
LOCALITY	New Orleans			Tennessee		Galveston	Galveston	New Orleans	Chicago
	W	N		W	N				
	%	%	%	%	%	%	%	%	%
HYPERTENSIVE	12.4	28.1	40.5	65.1	71.8	57.2	47.7	58.5	26.2
ARTERIOSCLEROTIC	12.3	8.4	20.7			20.2	13.7		24.1
SYPHILITIC	2.6	15.6	18.2	2.2	15.4	12.7	19.3	16.5	9.7
RHEUMATIC	4.7	6.4	11.1	15.3	4.3	3.4	7.3	17.6	29.2

evidence of pre-existing heart disease of any type. There were 14 cases of subacute bacterial endocarditis, 8 white patients and 6 Negro; 6 cases of acute bacterial endocarditis, 4 white patients and 2 Negro; one case (a white female) of acute suppurative myocarditis and pericarditis of postpneumonic origin; and one (a Negro female) of tuberculous pericarditis causing cardiac tamponade.

Anemia.—Seven deaths (0.7 per cent), 3 Negro patients and 4 white, were classified as due to anemia. Sickle cell anemia was the causative factor in the case of 3 Negro patients. Two were due to pernicious anemia, one to sprue, and one to chronic pulmonary hemorrhage.

Avitaminosis.—Five deaths (0.5 per cent) were classified as due to beriberi. Three of these patients were Negroes, and 2 were white. Three were females, and 2 were males. The age at death varied from 28 to 57 years.

Hyperthyroidism.—This condition caused 4 cardiac deaths (0.4 per cent). All of the patients were Negroes, and 3 of these were males. The age at death varied from 34 to 40 years.

Pulmonary Disease.—Four cardiac deaths (0.4 per cent), all among Negro patients, were attributed to primary pulmonary disease. Ayerza's disease was the cause of 3 deaths. The fourth was a case of chronic cor pulmonale secondary to pulmonary tuberculosis.

Other Types.—Under this classification we have included 3 deaths (0.3 per cent). Two were due to amyloidosis of the heart, and one was a case of acute dilatation of the heart caused by a rapidly given transfusion. All of these patients were Negroes.

Unknown.—Two Negro persons (0.2 per cent) died of heart disease of unknown origin: one had a diffuse, nonsuppurative, isolated myocarditis, and one had acute dilatation of the heart.

Trauma.—There was one death (0.1 per cent) due to a stab wound of the heart which severed the anterior descending coronary artery. This patient had a definite coincidental rheumatic lesion of the heart.

Combined.—This group consisted of 5 cases (0.5 per cent), 4 white patients and 1 Negro. A white woman, aged 78 years, had a syphilitic saccular aneurysm of the aortic arch, 6 cm. in diameter, which terminated in a dissecting aneurysm extending to the common iliac vessels.

were two age periods (10 to 15 years and 40 to 45 years) at which the highest rate of mortality occurred in the white race. There were similar peaks among the Negro patients, but these occurred 10 to 15 years later.

Complicating cardiac conditions in this group consisted of 16 cases of subacute bacterial endocarditis, 11 cases of arteriosclerosis, 5 cases of acute bacterial endocarditis, and 5 cases of hypertension.

Congenital.—Congenital cardiac lesions were the cause of 23 deaths, or 2.2 per cent of the total number of cardiac deaths. Fourteen of these persons were Negroes. The age at death varied from stillborn to 16 years. There were 15 females and 8 males. Further consideration of the varied anomalies included in this group would be too lengthy and detailed for this report. However, it is interesting that subacute bacterial endocarditis was present in only one case in this group.

Toxic.—Twenty-two deaths (2.1 per cent) were ascribed to toxic heart disease. Of these, 13 patients were white and 9 Negro (Fig. 2). The causes of the toxemia which produced these cardiac deaths were diphtheria, 12 cases; typhoid fever, 4 cases; septicemia, 2 cases; pertussis, 2 cases; bronchopneumonia, 1 case; and digitalis poisoning, 1 case.

Bacterial Infection.—Primary bacterial infection of the heart resulted in 22 (2.1 per cent) cardiac deaths. In none of these cases was there

TABLE I

SHOWING THE INCIDENCE OF EACH ETIOLOGICAL TYPE OF HEART DISEASE AS THE PRIMARY CAUSE OF DEATH, AND ALSO THE FREQUENCY WITH WHICH IT WAS PRESENT AS AN ASSOCIATED ABNORMALITY

	PRIMARY CAUSE OF DEATH		ASSOCIATED ABNORMALITIES PRESENT WHEN DEATH WAS DUE TO FOLLOWING TYPES OF HEART DISEASE						TOTAL IN THIS SURVEY	
ETIOLOGICAL TYPE OF HEART DISEASE	NUMBER	PERCENTAGE	HYPERTENSIVE	ARTERIOSCLEROTIC	SYPHILITIC	RHEUMATIC	COMBINED	TRAUMA	NUMBER	PERCENTAGE
Hypertensive	423	40.5	–	47	5	5	1	–	481	46.0
Arteriosclerotic	217	20.7	143	–	13	11	3	1	287	27.6
Syphilitic	190	18.2	8	3	–	–	2	–	203	19.4
Rheumatic	117	11.1	17	10	14	–	4	1	163	15.6
Congenital	23	2.2	–	–	–	–	2	–	25	2.4
Toxic	22	2.1	–	–	–	–	–	–	22	2.1
Bacterial infection	22	2.1	–	–	6	21	2	–	51	4.9
Anemia	7	0.7	–	–	–	–	–	–	7	0.7
Avitaminosis	5	0.5	–	–	–	–	–	–	5	0.5
Combined	5	0.5	–	–	–	–	–	–	5	0.5
Hyperthyroidism	4	0.4	–	–	–	–	–	–	4	0.4
Pulmonary disease	4	0.4	–	–	–	–	–	–	4	0.4
Other types	3	0.3	–	–	–	–	–	–	3	0.3
Unknown	2	0.2	–	–	–	–	–	–	2	0.2
Trauma	1	0.1	–	–	–	–	–	–	1	0.1

of the country, including Mexico. In this survey, hypertensive and arteriosclerotic heart disease caused death in 640 cases, or 61.2 per cent of the total number of cardiac deaths. This includes 190 cases (18.1 per cent) in which both conditions were present.

The greatest percentage of deaths due to syphilitic heart disease was in the Negro race; the ratio was roughly 6:1. There were four times as many males as females, considering both races. The incidence of this disease in this survey was about the same as in other reports originating in the South, but is much higher than that reported from Northern clinics, as would be expected.

The incidence of rheumatic heart disease was found to be higher than in 4 out of 6 reports originating in Southern states, but was much less than in the Northern states. It is interesting that Chavez[16] found an incidence of 41 per cent in Mexico City. This again would tend to disprove the common belief that rheumatic heart disease is rare in semitropical and tropical regions.

SUMMARY

Autopsy observations in 1,045 cases of death due to heart disease at the Charity Hospital of Louisiana in New Orleans over a period of six years were studied statistically. Table III gives the etiological distribution of these deaths in order of frequency:

TABLE III

ETIOLOGY	NUMBER	PERCENTAGE
Hypertensive heart disease	423	40.5
Arteriosclerotic heart disease	217	20.7
Syphilitic cardiovascular disease	190	18.2
Rheumatic heart disease	117	11.1
Congenital heart disease	23	2.2
Toxic heart disease	22	2.1
Bacterial infection	22	2.1
Anemia	7	0.7
Avitaminosis	5	0.5
Combined	5	0.5
Hyperthyroidism	4	0.4
Pulmonary disease	4	0.4
Other types	3	0.3
Unknown	2	0.2
Trauma	1	0.1

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…ES OF HEART DISEASE IN DIFFERENT GEOGRAPHICAL AREAS

…ortes[8]	White and Jones[4]	Geiger et al.[11]	Chavez[16]	Viko[12]				Clawson[19]
… York	New England	San Francisco	Mexico	Virginia	New York City	New England	Rocky Mountains	Minneapolis
%	%	%	%	%	%	%	%	%
1.1	29.2	6.8	13.6	32.6		21.7	14.9	55.5
8.1	35.7	24.9	28.3	32.4	22.3	26.3	21.1	6.2
4.6	3.9	7.2	11.2	7.8	8.6	2.7	1.1	7.0
7.2	39.5	22.2	41.0	15.6	42.7	29.3	41.0	18.6

A Negro man, aged 55 years, showed evidence of rheumatic, hypertensive, and arteriosclerotic heart disease, with fenestration of the cusps of the aortic and pulmonary valves and an aneurysm of the right coronary artery 2.5 cm. in diameter. A white man, aged 76 years, was found to have rheumatic and syphilitic valvular lesions and coronary arteriosclerosis. Two white women, 23 and 30 years of age, had congenital and rheumatic heart disease complicated by subacute bacterial endocarditis.

Table I shows the frequency with which each etiological type of heart disease was present as an associated abnormality and as primary cause of death.

DISCUSSION

It must be remembered that the majority of previous reports are based on clinical data only, whereas this report is based on autopsy observations in cases in which death was due to heart disease. Table II compares our observations with selected representative reports from different geographical areas. Only the four most frequent etiological types of heart disease are considered.

The hypertensive group includes over twice as many Negroes as whites, and the males predominate in both races. The peak of the number of deaths according to age begins approximately 20 years earlier in the Negro race than in the white race (40 years of age as compared to 60 years), and declines at approximately the same age (75 years of age in each). The high incidence of hypertensive heart disease in this survey of autopsy cases verified the similarly high clinical incidence reported from the Southern states.[3, 5, 9, 15] Here the high percentage of Negro patients is undoubtedly an important factor.

In the group in which death was due to arteriosclerotic heart disease there were more white than Negro patients. About one-half (59.3 per cent) of this group showed evidence of myocardial infarction, coronary occlusion, or both. In this select group the proportion of males to females and white to Negro patients was practically the same. The age distribution in the entire group was also practically the same in the white as in the Negro race. Arteriosclerotic heart disease was found to occur with similar frequency in reports from practically every section

INCIDENCE OF HEART DISEASE AND RHEUMATIC FEVER IN SCHOOL CHILDREN IN THREE CLIMATICALLY DIFFERENT CALIFORNIA COMMUNITIES

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CAPTAIN PAUL T. HAHMAN, M.C., ARMY OF THE UNITED STATES,
WILTON L. HALVERSON, M.D., AND MARGERY C. SHEARER, M.D.

THIS survey was planned primarily to show the influence of climate on the incidence of rheumatic heart disease and rheumatic fever.* General impressions are given of the economic status of each community studied, but it was not possible to segregate the children according to economic strata. An attempt was made to show by history, physical examination, and home visits the relation to rheumatic disease of age, sex, race, family history, diet, housing, previous and current infections, nutritional state, and other physical characteristics of the children.

The reporting of congenital cardiovascular defects, functional heart murmurs, and hypertension was incidental to the above objectives. Likewise, the discovery of previously undiagnosed cases was reported through the school nurses to the private physicians or health departments for follow-up and care. It is hoped that with projected improvement of environmental conditions, especially housing, the data from these surveys may be used for comparison with future surveys in evaluating the results of such community improvements.

Many school cardiac surveys have been made in the United States and Great Britain,[1-20] and the prevalence of rheumatic disease in children has likewise been ascertained from the compulsory notification of rheumatic fever in Norway, Sweden, Denmark, Iceland, and certain cities in Germany and England.

Considerable differences have been reported in the prevalence of heart disease, ranging from 0.3 to 2.6 per cent, not only in different locales but even in the same community. This has been dependent on the following factors: (1) A difference in diagnostic criteria; (2) variation of the degree of skill and interest of the examiners; (3) irregular selection of samples from different age groups; (4) unawareness of socio-economic influences affecting certain groups; and (5) exclusion of children too ill to attend the schools where the examinations were made. The first four of these possible errors of survey technique we believe have been

From The California State Department of Public Health and The California Heart Association.

Received for publication April 24, 1944.

*The term "rheumatic fever" is used herein to include all recognized phases of the disease which are termed by some investigators, most notably Coburn, as the "rheumatic state." Further definition of this term will be given under the review of the criteria used for diagnosis. Rheumatic heart disease is the term applied to all positively diagnosed rheumatic, mitral, or aortic valvulitis which is not obviously associated with other congenital heart defects.

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miles north of San Francisco. It is in "the heart of the Redwood Empire," and also in the center of a large dairy-farming region, so that its livelihood comes from lumbering, fishing, and agriculture. Redlands, the next largest, is an inland town in San Bernardino County about 80 miles southeast of Los Angeles. It is the center of a large navel-orange growing belt, and its prosperity fluctuates largely with the condition of the Eastern orange market. Susanville, the smallest town, is the county seat of Lassen County, and is in the center of a large pine-lumbering district. It is on the eastern slope of the Sierra Nevada Mountains, about 320 miles northeast of San Francisco and 85 miles northwest of Reno, Nevada.

CLIMATICOLOGIC DATA

The following tables show the variations in climatic data in the three towns over the four-year period of 1937, 1938, 1939, and 1940.

Table I gives the average annual mean temperature (degrees Fahrenheit), average total precipitation (in inches), average total snowfall

TABLE I

Town	County	Elevation (ft.)	Temperature (°F.): Length of record (yr.)	Temperature (°F.): Average annual mean	Precipitation (in.): Length of record (yr.)	Precipitation (in.): Average annual total	Precipitation (in.): Average total snowfall (unmelted)	Number of days: Clear	Number of days: Partly cloudy	Number of days: Cloudy	Number of days: With precipitation 0.01 inch or more
Eureka	Humboldt	44	47	52.7	52	42.44	Tr	75	98	192	118
Redlands	San Bernardino	1352	48	62.6	52	17.10	0	264	64	37	46
Susanville	Lassen	4268	43	50.7	43	21.27	55.5	187	68	110	73

TABLE II

AVERAGE MEAN TEMPERATURE, BY MONTHS, FOR THE FOUR YEARS

Town	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Annual
Eureka	48.7	48.9	50.1	51.8	53.6	54.7	57.4	57.2	58.4	56.2	51.1	50.8	52.7
Redlands	48.9	49.7	54.3	60.3	64.8	70.3	75.7	76.4	73.3	65.4	57.1	54.9	62.6
Susanville	30.2	32.0	41.1	49.4	57.6	65.0	70.8	70.1	61.4	51.6	39.4	36.9	50.75

TABLE III

AVERAGE TOTAL PRECIPITATION, IN INCHES, BY MONTHS, FOR THE FOUR YEARS

Town	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Annual
Eureka	4.69	8.77	8.22	1.93	1.77	0.48	0.04	0.02	0.78	3.59	3.64	8.66	42.44
Redlands	2.52	3.91	3.86	1.44	0.23	0.01	0.02	0.00	0.87	0.56	0.58	3.10	17.10
Susanville	3.62	5.74	4.08	0.62	0.59	0.46	0.27	0.03	0.29	0.85	2.35	3.36	21.27

obviated. However, these surveys support the general belief that rheumatic fever is prevalent in temperate zones,[21, 22, 23] and especially in moderately high altitude areas such as Mexico City and the North Central Plains and Rocky Mountain Regions of the United States,[24] where extremes of temperature are common. Although the disease is uncommon in certain tropical and semitropical regions, such as the Caribbean Area and the Southern United States,[23, 25, 26] other localities in the tropical zones fail to show such immunity. These are most notably Ceylon,[27] Northern Australia,[28] and, judging from recent verbal reports of military officers, the islands in the tropical South Pacific area.

Insofar as some of the data in this paper support the suggestion, the disease has been thought to be more insidious in its onset in certain warmer climates, leaving in its wake unexplained valvulitis. There are considerable differences in the frequency of past histories of rheumatic fever among rheumatic cardiacs surveyed in different parts of this country.[23]

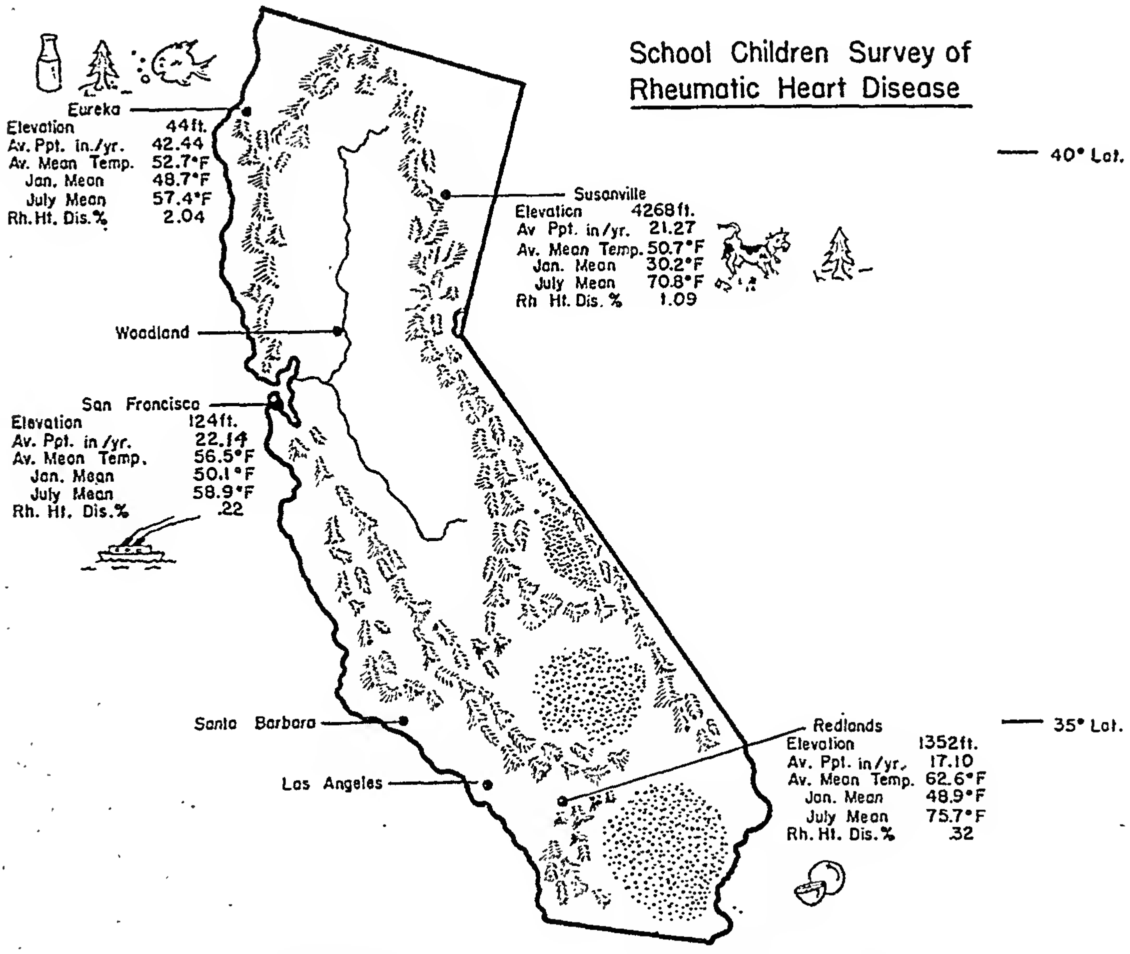

Fig. 1.—Map of California showing approximate location of towns of survey.

LOCALE FOR STUDY

The communities chosen for study were Eureka, Redlands, and Susanville; a brief description of each follows:

Eureka, the largest of the three towns, is the county seat of Humboldt County, and is located on Humboldt Bay on the Pacific Coast about 250

group, who derive their income primarily from the payrolls of the two lumber mills near the town.

After consulting various agencies,* no definite figures could be found on the socio-economic scale of living for the three towns, but Table IV might be of some interest and significance.

The figures in Table IV are not strictly comparable because Susanville is included with all of Lassen County. The large number of wholesale employees in Redlands are probably fruit packers and workers in the orange industry.

DESCRIPTION OF THE SCHOOL SYSTEMS

Eureka.—The school system consists of three public kindergartens; six public primary schools, first through sixth grades; one parochial school, kindergarten through eighth grades; one junior high school, grades 7. 8, and 9; and one Union Senior High School. The school population at the end of the 1940 school year was approximately as follows:

Public primary schools	1,432
Catholic parochial school	390
Junior high school	747
Senior high school	968
Total	3,537

The examinations were carried out in all but the seventh and eighth grades of the parochial school, so that all social and age groups were fully represented. A total of 2,703 pupils, or 76.6 per cent of the school population, were examined, plus thirty-four children of preschool age.

Redlands.—The school system consists of six public primary schools, kindergarten through sixth grades; one junior high school; one senior high school; and one parochial school. The exact distribution of the children in the various schools is not known, but the total public school population in June, 1939, was 3,669. During the spring of that year, 2,013 children were examined; a sample group was taken from all grades, with an approximately equal distribution for both age and social groups. In February and March, 1941, 562 new pupils in the kindergartens and first and fifth grades were examined, plus 177 pupils who had been in the 1939 group. These 177 were made up of 115 normal children who were re-examined in the fifth grade, and 62 out of 129 cardiac suspects who were found in the 1939 examinations and could still be in school in 1941. Roughly, then, 2,574 children were examined in 1939 and 1941 out of a total of approximately 4,223 pupils, or 60.8 per cent of the public school population.

Susanville.—The school system consists of four elementary schools, kindergarten through the eighth grade, and one combined Union High School and Junior College. The population of the elementary schools was 863 pupils at the close of the 1941 school year, whereas that of the

*California Department of Public Health, California Chamber of Commerce, California Medical Association, California Social Welfare Bureau, California Bureau of Labor Statistics, State Department of Epidemiology Statistics.

(unmelted), and average number of clear, partly cloudy, and cloudy days, and the average number of days with a precipitation of more than 0.01 inch for the year. It also gives the elevation of the town above sea level, and the length of record, i.e., number of years, that a weather station has been established in each town.

Table II gives the average mean temperature by months for the four-year period; Table III gives the average mean precipitation by months, snowfall not included, for the same years. Data for the mean relative humidity were not available for the three towns.

It can readily be seen from these tables that Eureka has a rather mild, constant temperature, but is quite damp, whereas Redlands may be considered as warm and fairly dry, with its rainfall coming in the winter months. Susanville has rather typical California "mountain climate"; it is quite cold in the winter, but hot in summer, and has only a moderate precipitation, most of which comes in the late winter and early spring.

DESCRIPTION OF POPULATION*

Eureka.—According to the 1940 census, the population of Eureka is 17,055 persons, consisting primarily of native-born whites of Scandinavian parentage, with a few Italians and Portuguese. There are no Chinese or Japanese, and only one or two Negro families.

TABLE IV

ECONOMIC INDEX OF TOWNS

TOWN	RETAIL TRADE 1939		WHOLESALE TRADE 1939		SERVICE ESTABLISHMENTS 1939				INCOME TAX RETURNS FILED 1938	
	NUMBER OF STORES	SALES ADD. 000	NUMBER OF ESTABLISHMENTS	NUMBER OF EMPLOYEES, AVERAGE FOR YEAR	TOTAL PAYROLL ADD. 000	NUMBER OF ESTABLISHMENTS	NUMBER OF EMPLOYEES, AVERAGE FOR YEAR	TOTAL PAYROLL ADD. 000	NUMBER	1940 POPULATION (%)
Eureka	390	11,749	46	219	328	165	169	174	1,442	8.45
Redlands	226	5,947	24	942	772	83	141	147	910	6.35
Lassen County*	208	5,631	18	58	93	44	62	70	341†	21.65

*Population, 14,479 (1940).

†Figure is for Susanville; it probably includes residents of County filing within City limits, but not living there.

Redlands.—The population of Redlands, by the 1940 census, is 14,324; the majority are whites, with a fair proportion of Mexicans, and a smaller group of Italians, Portuguese, and Negroes.

Susanville.—By the 1940 census, Susanville has 1,575 persons living within the city limits. The majority are whites, with a small percentage of Chinese and Negroes. The people are mostly of a stable, working

*There are no accurate figures on the population breakdown as to races, etc., according to the 1940 census. Those of 1930 are unreliable because of migration.

Fig. 2 is a sample form used for recording the histories and physical examination.

CARDIAC SURVEY

Town -------------------------- Date ---------- Schedule Number ----------
Name ------------------------------ Age ---- Sex ---- Nationality ---------
Address ------------------------- Duration in town of survey ---- mo; ---- yr.
School --------------------------, grade ------; Religion ----------; Designate other localities and dates in which residence has been maintained since birth ------
----

Family history—cases cardiac or rheumatic state ----------------------------
Personal history. Average hours sleep per day ----; adequate clothing ----------
Diet—milk ----, fruit ----, vegetables ----, protein ----, carbohydrates ----
Special comments ---
General health—tonsil and adenoid infection ---------; frequent colds ---------;
Dyspnea ------; fatigue ------; palpitation ------; sweats ------; history blue baby ------; other cardiac conditions ---------------------------------
Illness history (indicate age or year of occurrence and successive attacks)

Rheumatic fever --------; Rheum. pains {bone --------; joint --------; muscle --------}; Chorea --------
Subq. nodules ------------; Nose bleeds ------------; Purpura ------------
Tonsillitis ----------; Otitis media ----------; Erythematous rash ----------
Scarlet fever --------; Diphtheria ----------; Other ----------------------

Home—No. rooms ----, No. sleeping rooms ----, No. with sunshine available ----
No. rooms with heat ----; type heating unit ----------; general sanitation----
-------------------------; drainage on premises ----------------------

Physical examination—height ------; weight ------; temp. ------; nutrition standard -----; pallor -----; scoliosis -----; chest shape -----; throat inf. -----; dental caries ------; infection ------; lungs ------; lymph gl. cervical -----; heart apex. imp. ------ cm.; ------ mcl.; thrill --------
sounds—P_2----------- A_2----------- Murmurs ----------- Rate -----------
Rhythm ------------------ Blood pressure R------ L------, B.P. legs------
Periph. vessels ------------------------------.

Fig. 2.

METHOD OF EXAMINATION

The children were brought to the examining room in groups of three or four of one sex, where they all stripped to the waist; large towels were given to the girls to drape over their shoulders. The height and weight measurements were then recorded, with the children's shoes left on to facilitate and speed the examination. When necessary, approximate deductions were made for boots and rubber or other heavy-soled shoes. Each child's nutrition was checked with the Faber "Weight-Height-Age Table for California School Children" (prepared for the San Francisco Tuberculosis Association),[29] which gives the normal height and weight range by sex for the ages of 5 to 15 years, inclusive. Any variation from the normal was recorded on the charts by the number of pounds above or below the normal figure for the given sex, age, and height.

The examiner sat with his back to a window, using only daylight for the examination, which was carried out as follows:

Inspection.—The examiner inspected the child in general to detect the presence or absence of pallor, cyanosis, scoliosis, or any marked chest

combined High School and Junior College was roughly 550 pupils. Because of local conditions and lack of time, examinations were carried out only in the elementary schools; a total of 838 pupils, or 97 per cent of the elementary school population, was examined. Thus this does not represent all age groups. All social groups were well represented.

PROCEDURE FOR THE SURVEY

The personnel for the survey consisted of: (1) a physician (Hahman), who carried out the examinations, read the roentgenograms and electrocardiograms, and made the diagnoses on all of the children; (2) a trained assistant, who took the height and weight measurements, brought the children to the examining room, and kept the records during the survey; and (3) a Public Health Nurse, assigned especially to the survey by the California State Department of Public Health, who made the home visits, assisted in taking the children to and from the roentgenographic laboratory, and, after training, took part of the histories.

The personnel was the same for all the surveys except that the work in Redlands, in 1939, was done by a second physician (Shearer), and the histories of the children in the Eureka Primary schools were not taken by the same Public Health Nurse who took those in the Eureka Junior and Senior High Schools and in the Redlands (1941) and Susanville schools.

The rest of the procedure, methods of examination, and criteria for diagnosis were the same for the three towns except for that part done in Redlands in 1939. The latter, however, closely paralleled those of the 1940 to 1941 survey, and the results, as far as the incidence of organic heart disease is concerned, are comparable.

The examinations of the children were carried out at the various schools in a relatively quiet, light, airy room which had been set aside for that purpose. Slips were sent by the schools to the parents for their consent for the physical examination, and, later, consent for laboratory study, that is, roentgenograms and electrocardiograms when necessary.

The time and date of the examinations were given to the parents, and their presence at the schools was encouraged. A complete history, with emphasis on facts pertaining to the etiological factors of rheumatic heart disease, and to the child's environmental conditions, was obtained for all the children examined. These histories were taken principally by the Public Health Nurse on her home visits, but, in about one-sixth of the cases, in Eureka especially, the histories were obtained from the parents at the time of the examination, or, in the older group, from the children themselves.

There was a small group of children that moved away from town after the examination, or whose parents refused to give the histories, and therefore those cases were discarded in tabulating the results of the survey.*

*Children confined at home were not included in the survey, and such cases, although rare, alter the sample of the population studied.

offices of the local radiologists. Electrocardiograms were not taken on the small group of Redlands children (eleven) who were sent for roentgenograms in the 1940 survey (Hahman).

CRITERIA FOR DIAGNOSIS

The following definitions were used in the diagnosis and classification of the various murmurs or conditions found during the survey.

1. *Normal.*—Any child without a history of rheumatic fever, rheumatic joint, bone, or muscle pains (so-called "growing pains") or chorea, and with no heart murmur at the time of the examination was classified as "normal."

2. *Functional.*—Any child with a soft systolic murmur over the precordium that varied with respirations and change of position, became louder after exercise, and was not transmitted to the back, neck, or axilla was classified as "functional." This diagnosis was also used in those cases in which there was a marked variation in the murmurs as heard during the first examination and as heard again at the time of the recheck. No attempt was made to segregate the so-called "accidental" and "cardiorespiratory" murmurs from the "functional" murmurs due to anemia, recent fever, or other possible cause. "Functional," therefore, as used in this survey, denotes those murmurs which were thought definitely to be "nonorganic" in the broadest sense of the term, as opposed to the "organic" murmurs of congenital or rheumatic origin which, we presuppose, are associated with definite, and probably permanent, vascular, myocardial, or valvular deformity.

3. *Potential Rheumatic* (rheumatic fever without evident heart disease).—In this group were those cases in which there was a history of one of the primary manifestations of rheumatic fever, namely, acute polyarthritis, chorea, or recurrent bone, joint, or muscle pains, but without any evidence of organic heart disease or active infection at the time of the examination.

4. *Rheumatic Fever History.*—Cases in which there was a history of one of the primary rheumatic manifestations, or a history of two or more of the secondary manifestations, e.g., recurrent tonsillitis or torticollis, purpura, frequent, unexplained, severe epistaxis, various erythemata, and subcutaneous nodules were included in this group.

a. With valvulitis: Definite evidence of one or more of the following: aortic insufficiency and/or stenosis, mitral insufficiency and/or stenosis (pulmonary and tricuspid valvular lesions not to be considered rheumatic in absence of mitral valve lesions).

b. With probable heart disease: Myocarditis with above criteria for rheumatic fever.

5. *Mitral and/or Aortic Valvulitis.*—This group did not include cases of congenital or syphilitic heart disease.

a. Rheumatic heart disease without a rheumatic fever history. Cases in which there were signs of mitral or aortic valvulitis without any known history of previous infection.

b. With scarlet fever history: Cases in which there were signs of valvulitis, as previously mentioned, without history of rheumatic infection, but with definite history of scarlet fever at some time prior to the date of examination or prior to the discovery of a murmur by a local physician.

6. *Congenital Heart Disease.*—This group included those cases in which there were characteristic physical signs, with confirmation by roentgenogram and electrocardiogram.

deformity. Absence was noted by an "O" sign; presence and its degree of severity by the plus sign and its multiple. Any chest deformity was described, and the degree of severity noted as mild, moderate, or severe.

The mouth and throat were then inspected, with the aid of a tongue blade, for the presence of caries, mouth infection, and particularly throat infection and tonsillar enlargement. Any variations from normal were again recorded by the signs "one, two, or three plus" as follows: (1) *Dental caries,* +, one or two teeth with small cavities; ++, at least two teeth with moderately large cavities, or three or four with small cavities; and +++, four or more teeth with cavities of moderate size, or three or four with huge cavities. (2) *Throat infection* +, red, inflamed fauces, tonsils out or not appreciably enlarged; ++, almond- to chestnut-sized tonsils without evident infection; +++, above size with evident infection, or huge tonsils that filled the posterior pharynx.

Palpation.—(1) Palpation of the neck was used to detect any enlargement of the cervical lymph nodes. (2) Palpation of the chest was used to detect the presence of a thrill and to locate the point of maximum apical impulse (PMI). The distance of the PMI and midclavicular line from the midsternal line was then measured with a centimeter rule, the measurements recorded, and a comparison of the two was used as an indication of the heart size. If the midclavicular point was not less than the distance of the PMI from the midsternal line, the heart was considered to be of normal size. Displacement of the heart, as by scoliosis, was evaluated.

Percussion.—Percussion was used only when a child was suspected of having a lung disease or heart enlargement, as noted by the position of the PMI.

Auscultation.—(1) Auscultation of the lungs was used to ascertain the presence or absence of "squeaks," râles, or rubs, and (2) of the heart, in the standing and supine positions, to ascertain the cardiac rate and rhythm, the quality and intensity of the heart sounds, and the presence of murmurs or other abnormal sounds. The rate was counted in all cases while the patient was lying on the examining table; the auscultatory method was used, and the number of apical beats was counted for at least a fifteen-second interval.

Any child suspected of having heart disease was also examined after exercise, which consisted of jumping up and down fifteen to twenty times on each foot, and in the sitting and left lateral positions. A notation was also made of the presence of any abnormal sounds over the peripheral vessels.

The blood pressure was taken on all the children in the supine position at the conclusion of the examination. A 12 cm. cuff was used on the right arm, and was found to be of satisfactory size for all but the smaller children, of 5 years or under, and for the markedly obese of 14 years or older. In any case in which disease was suspected, the pressure was also taken on the left arm, and on the legs when necessary. Any child with a brachial systolic blood pressure greater than 140 mm. Hg, without obvious signs of undue nervousness, was brought back at a later date, when possible, and the pressure retaken.

Any child who was found to have signs of an organic heart lesion, but who had a negative history of rheumatic fever, and in whom the diagnosis was not certain, was brought back for re-examination at a later date. If the diagnosis was still doubtful, roentgenograms and electrocardiograms were made when possible; this work was done at the

Tables V and VI present the total figures for the entire survey, and show the comparison of the "S" and "H" studies and the effect of exclusion of 447 cases in which there were no histories or no established residence of over two years in the community. The results of the grand total are chiefly important in the number of congenital heart lesions and functional murmurs, for those figures are probably not influenced by residence or inadequate histories in Table VII. Since the method of history taking was faulty in the 1939 Redlands "S" survey, all of the figures on the "S" survey are to be discounted where history is concerned, as in "Potential Rheumatic Heart Disease," or "Rheumatic History in Cases of Rheumatic Heart Disease."

The incidence of 0.7 per cent of congenital heart disease is comparable with the 0.65 per cent found after exclusion of the 447 cases mentioned. This is a high incidence when compared to many previous surveys, but is not greatly different from that found by Sampson, Christie, and Geiger,[17] in San Francisco, in 1938.

The incidence of 16.6 per cent of functional murmurs may seem to be low. The incidence of rheumatic heart disease and total rheumatic cases of 1.3 per cent and 1.9 per cent, respectively, is unusually high for what has been considered an area in which endemic rheumatic disease is rare. As is shown in Tables VIII and IX, this is due to the fact that a larger population was examined in Eureka and Susanville, which together somewhat exceed Redlands. The figures of 1.17 per cent rheumatic heart disease and 1.7 per cent total rheumatic heart disease, as obtained from the entire series after exclusion of the 447 cases, probably indicate more accurately the actual incidence of these conditions. Likewise, the percentage of congenital heart disease is more accurately indicated by 0.65 per cent, and of total organic heart disease by 1.82 per cent.

The data presented in Table VI indicate that care must be exercised in reporting local surveys to exclude cases in which rheumatic disease may have been acquired elsewhere.

Table VII, a summary of the Redlands surveys, shows a fair agreement between the "S" and "H" reports in the incidence of congenital heart disease, but a considerable disagreement in the percentage of rheumatic potential and actual heart disease. This can probably be explained in three ways: (1) differences in personal interpretation of observations; (2) selection of only certain school grades in the "H" study; and (3) "chance" in dealing with such small figures, i.e., only ten rheumatic cases in the "S" survey and five in the "H" survey.

In spite of these differences, the total figure of 0.19 per cent potential, and 0.38 per cent rheumatic, heart disease, and 0.57 per cent total rheumatics is a significantly low incidence. This is as may be expected in the warm, dry climate of Redlands.

In reference to Susanville, Table VIII, the population was smaller, and, therefore, the figures are more subject to statistical misinterpreta-

7. *Hypertension.*—This diagnosis denotes probably only a transient affair, and cannot be considered as true hypertension in all cases. Using the reports of Faber and James,[30] Taussig and Hecht,[31] and others, the maximal blood pressures for given age groups were set as follows: (a) 5 to 9 years, inclusive, 120/80; (b) 10 to 14 years, inclusive, 130/85; and (c) 15 years and over, 140/90.

Whenever a diagnosis of hypertension was then made, it was classed as an incidental finding, and not as the primary diagnosis.

8. *Unclassified Group* (classification unknown).—In this group were those cases in which there was no history of rheumatic fever, but in which there were murmurs which did not definitely fit any of the above criteria, and in which the roentgenograms and electrocardiograms were normal or of no diagnostic value. According to the type, quality, and location of the murmur, the cases were classified as follows: (a) rheumatic vs. functional, (b) congenital vs. functional, and (c) rheumatic vs. congenital.

Certain cases of organic heart disease undoubtedly are included in this group.

9. *Positive Family History.*—Those cases in which there was a history of rheumatic fever or chorea, or rheumatic heart disease in the immediate family or in some person or relative in intimate daily contact with the patient were classified as having "positive family history." This was also an incidental diagnosis, and is classed with one of the previously mentioned primary diagnoses.

The data obtained from the histories and physical examinations were assembled by the Statistical Division of the California State Department of Public Health in five sets of tables, twelve to a set. The sets were for: (1) The Shearer Redlands Survey of 1940; (2), (3), and (4) The Hahman Surveys of Redlands, Eureka, and Susanville of 1940 and 1941; and (5) the total of the Hahman surveys. The titles of the original tables of each set were:

Table I, "Showing Distribution and Percentage by Diagnosis;" Table II, "Showing Distribution and Percentage by Age and Diagnosis;" Table III, "Showing Distribution and Percentage by Sex and Diagnosis;" Table IV, "Showing Distribution and Percentage by Race and Diagnosis;" Table V, "Distribution and Percentage of Those With a Positive Family History in Each Diagnostic Group;" Table VI, "Distribution and Percentage of Diagnostic Groups According to Food Consumption;" Table VII, "Evaluation of Housing Conditions, Showing Distribution and Percentage for each Diagnostic Group;" Table VII-A, "Evaluation of Housing Conditions Based on Crowding Alone, Showing Distribution and Percentage for Each Diagnostic Group;" Table VIII, "Distribution and Percentage of Hypertension in Diagnostic Groups;" Table IX, "Distribution and Percentage of Selected Points of Physical Examination for Each Diagnostic Group;" Table X, "Distribution and Percentage of Nutritional Standards by Diagnostic Group;" Table XI, "Distribution and Percentage of Certain Organic Troubles by Diagnostic Group;" Table XII, "Frequency of Upper Respiratory Infections and Incidence of Various Diseases by Diagnosis."

DISCUSSION OF DATA

The data from some of these tables have been reorganized, and the following constitutes a discussion of the material contained in these revised tables. In reproduction of tables, the letters "S" and "H" indicate Shearer or Hahman as the surveyor.

TABLE VI

ANALYSIS OF 447 CASES EXCLUDED FROM TABLE V

	TOTAL NUMBER CASES	NORMAL WITHOUT MURMUR	NORMAL WITH FUNCTIONAL MURMUR	NORMAL TOTAL	UNCLASSIFIED	CONGENITAL HEART DISEASE	POTENTIAL RHEUMATIC HEART DISEASE	RHEUMATIC HEART DISEASE	TOTAL RHEUMATIC CASES	TOTAL ORGANIC HEART DISEASE
Length of residence unknown	11	5	5	10	1	-	-	-	-	-
Residence less than two years	406	303	87	390	4	5	3	4	7	9
Rheumatic illness not contacted in area	14	-	-	-	-	-	5	9	14	9
Examined but history refused	16	-	16	16	-	-	-	-	-	-
Total cases	447	308	108	416	5	5	8	13	21	18
Percentage	100	69	24.3	93	1.1	1.1	1.8	2.9	4.7	4

TABLE V

SUMMARY OF 1939 AND 1940 TO 1941 SURVEYS IN REDLANDS, EUREKA, AND SUSANVILLE, CALIFORNIA

		TOTAL	NORMAL WITHOUT MURMUR	NORMAL WITH FUNCTIONAL MURMUR	NORMAL TOTAL	UNCLASSIFIED	CONGENITAL HEART DISEASE	POTENTIAL RHEUMATIC HEART DISEASE	RHEUMATIC HEART DISEASE	TOTAL RHEUMATIC CASES: RHEUMATIC HISTORY POS.	TOTAL RHEUMATIC CASES: RHEUMATIC HISTORY NEG.	TOTAL RHEUMATIC CASES	TOTAL ORGANIC HEART DISEASE
All children examined, including Redlands 1939 "S" survey and 447 cases of Table VI; Redlands (2,698), Eureka (2,719), and Susanville (832)	Number of cases	6,249	4,972	1,036	6,008	77	43	38	81			119	124
	Percentage	100	79.5	16.6	96.1	1.2	.7–	.6+	1.3			1.9	2
1939 "S" survey of Redlands (2,012) and 1940 to 1941 "H" survey of Redlands (686), Eureka (2,719), and Susanville (832); *excluding* 447 cases of Table VI	Number of cases	5,802	4,664	938	5,602	64	38	30	68			98	106
	Percentage	100	80	16.1	96.1	1.1	.65	.52	1.17			1.7	1.82
1940 to 1941 "H" survey of Redlands, Eureka, and Susanville	Number of cases	3,790	2,779	835	3,614	63	25	26	62	22	40	88	87
	Percentage	100	73	22	95	1.66	.66	.68	1.63	.58	1.06	2.32	2.29

tion. This is especially so with congenital heart disease, with only three cases and a percentage incidence of 0.4 per cent, about two-thirds of the incidence of the whole group. The high frequency of rheumatic fever (including rheumatic heart disease), and rheumatic heart disease, namely, 2.6 per cent and 1.1 per cent, seems to be significant statistically. This community has a climate not unlike the high altitude communities of Salt Lake City and Denver, both of which are now known to have high rheumatic fever morbidity and mortality rates.

Eureka, Table IX, with its remarkably uniform, cool, damp climate, presents the highest incidence of rheumatic heart disease (2.0 per cent), although the less dependable figures of potential rheumatic heart disease and total rheumatic disease are respectively lower and equal to those of Susanville. Congenital heart lesions were nearly as frequent as in Redlands, 0.7 per cent (0.69+ per cent) compared to 0.76 per cent. Inasmuch as housing projects were under construction in Eureka and a general im-

TABLE VIII

SHOWING DISTRIBUTION AND PERCENTAGE BY DIAGNOSIS OF 732 CHILDREN IN SUSANVILLE*

	TOTAL	NORMAL WITHOUT MURMUR	NORMAL WITH FAMILY HISTORY OF RHEUMATIC FEVER	NORMAL WITH FUNCTIONAL MURMUR	TOTAL NORMAL	UNCLASSIFIED	CONGENITAL HEART DISEASE	POTENTIAL RHEUMATIC HEART DISEASE	RHEUMATIC HEART DISEASE WITHOUT HISTORY OF RHEUMATIC FEVER	RHEUMATIC HEART DISEASE WITH HISTORY OF RHEUMATIC FEVER	TOTAL RHEUMATIC HEART DISEASE	TOTAL RHEUMATIC DISEASE	TOTAL ORGANIC HEART DISEASE
Number	732	541	27	136	704	6	3	11	4	4	8	19	11
Percentage	100	73	3.7	18.6	95.3	0.8	0.4	1.5	0.5	0.5	1.1	2.6	1.5

*One hundred additional children were examined, but were excluded from this table because of residence of less than two years or because rheumatic fever was contracted elsewhere.

TABLE IX

SHOWING DISTRIBUTION AND PERCENTAGE BY DIAGNOSIS OF 2,450 CHILDREN IN EUREKA*

TOTAL	NORMAL WITHOUT MURMUR	NORMAL WITH FAMILY HISTORY OF RHEUMATIC FEVER	NORMAL, WITH FUNCTIONAL MURMUR.	TOTAL NORMAL	UNCLASSIFIED	CONGENITAL HEART DISEASE	POTENTIAL RHEUMATIC HEART DISEASE	RHEUMATIC HEART DISEASE WITHOUT HISTORY OF RHEUMATIC FEVER	RHEUMATIC HEART DISEASE WITH HISTORY OF RHEUMATIC FEVER	TOTAL RHEUMATIC HEART DISEASE	TOTAL RHEUMATIC DISEASE	TOTAL ORGANIC HEART DISEASE
2450	1662	57	585	2304	52	17	14	33	17	50	64	67
100	68	2.3	23.8	94.2	2.1	0.7	0.6	1.3	0.7	2	2.6	2.7

*One hundred additional children were examined, but were not included because of residence of less than two years, or because rheumatic fever was contracted elsewhere, or because of inadequate history.

TABLE VII

SUMMARY OF 1939 (S) AND 1940 TO 1941 (H) SURVEYS OF 2,663 CHILDREN IN REDLANDS

	TOTAL	NORMAL WITHOUT MURMUR	NORMAL WITH FUNCTIONAL MURMUR	NORMAL TOTAL	UNCLASSIFIED	CONGENITAL HEART DISEASE	POTENTIAL RHEUMATIC HEART DISEASE	RHEUMATIC HEART DISEASE	RHEUMATIC HISTORY POS.	RHEUMATIC HISTORY NEG.	TOTAL RHEUMATIC CASES	TOTAL ORGANIC HEART DISEASE
1939 (S) Redlands												
Number of cases	2,012	1,885	103	1,988	4	13	4	6			10	19
Percentage	100	93.6–	5.1	98.7–	.2	.64	.2	.3			.5	.94
1940 to 1941 (H) Redlands												
Number of cases	621	492	114	606	5	5	1	4	1	3	5	9
Percentage	100	79	18.3	97.3	.8	.8	.16	.65	.16	.48	.8	1.45
Total	2,633	2,377	217	2,504	9	18	5	10			15	28
Percentage	100	90.5	8.2	98.7	.34	.76	.19	.38			.57	1.14

TABLE X

SHOWING DISTRIBUTION AND PERCENTAGE BY SEX AND DIAGNOSIS
Total of 3,790 Cases, 1940 to 1941 Surveys (H)

SEX	TOTAL		NORMAL WITHOUT MURMUR		NORMAL WITH FAMILY HISTORY OF RHEUMATIC FEVER		NORMAL WITH FUNCTIONAL MURMUR		TOTAL NORMAL		UNCLASSIFIED		CONGENITAL HEART DISEASE		POTENTIAL RHEUMATIC HEART DISEASE		RHEUMATIC HEART DISEASE WITHOUT HISTORY OF RHEUMATIC FEVER		RHEUMATIC HEART DISEASE WITH HISTORY OF RHEUMATIC FEVER		TOTAL RHEUMATIC DISEASE	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Male	1,891	49.9	1,326	49.5	52	55.3	407	48.7	1,783	49.5	40	63.5	12	48.0	15	57.7	27	67.5	12	54.5	54	61.4
Female	1,899	50.1	1,359	50.5	42	44.7	428	51.3	1,831	50.5	23	36.5	13	52.0	11	42.3	13	32.5	10	45.5	34	38.6
Total	3,790	100.0	2,685	100.0	94	100.0	835	100.0	3,614	100.0	63	100.0	25	100.0	26	100.0	40	100.0	22	100.0	88	100.0

provement in living standards was occurring, a repetition of the survey in this city in five to ten years may show the influence of such social changes in the rheumatic disease incidence. All sets of tables are being retained for such possible comparison in future studies.

The report of a positive history of rheumatic fever in any of its manifestations occurred in 35 per cent of all cases of rheumatic heart disease, in 25 per cent of the Redlands cases ("H" survey), 50 per cent of the Susanville cases, and 35 per cent of the Eureka cases. With the exception of the Susanville report, these are lower figures than have been published previously in most surveys.[32, 33]

Tables X to XV deal with certain data on the consolidated reports of all three communities surveyed by Hahman. Similar tables, as previously stated, are available for each individual town, but their comparison was not considered of sufficient importance to be presented here.

Table X confirms more recent reports[11] that older males are affected with rheumatic disease more frequently than females, i.e., 61.4 per cent and 38.6 per cent, respectively. This is particularly evident in the group with rheumatic heart disease without a rheumatic history.

Table XI, on relation of race to rheumatic disease, shows how largely the population was composed of whites; the very few Negroes and most of the Mexicans were concentrated in Southern California (Redlands). As has been previously reported by Paul and Dixon,[34] the incidence of rheumatic disease in Indians living in northern temperate zones is high, and this was found in our survey; 4.6 per cent of the total rheumatic population was Indian, compared to 2.1 per cent of the normal population. Thus, 5 per cent of the whole Indian population had rheumatic disease, and 3.3 per cent had rheumatic heart disease. Mexicans did not seem to be especially susceptible, although the figures for Redlands, not given in a table, were 1 per cent of rheumatic disease in Mexicans, as contrasted to 0.57 per cent in the entire population. The number of cases in both of these racial groups is too small to draw any positive conclusion. The observations should be considered as only suggestive.

Table XII is presented to illustrate how infrequently a family history of rheumatic fever or rheumatic heart disease was obtained in this survey. Only 5.7 per cent of rheumatic children gave a positive family history, which was hardly a significant difference from the 3.6 per cent rheumatic family histories in the normal group. Reasonable care was exercised in obtaining family histories from parents, but the low figures, when compared to other reports,[35] throw some doubt on the accuracy of these histories.

Table XIII shows the effect of housing,* and of crowding, in particular, on the occurrence of rheumatic disease.[36-38] There was a recog-

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*Housing:

Good—1 or less person per room, and heat in over half of the rooms of the house: i.e., three rooms in a five-room house.

Fair—1 to 1½ persons per room, with heat in more than half of the rooms of the house.

Poor—More than 1½ persons per room, or 1 to 1½ persons per room, with heat in one-half the house or less.

TABLE XII

DISTRIBUTION AND PERCENTAGE OF THOSE WITH A POSITIVE FAMILY HISTORY OF RHEUMATIC FEVER IN EACH DIAGNOSTIC GROUP

Total of 3,790 Cases, 1940 to 1941 Surveys (H)

	TOTAL		NORMAL WITHOUT MURMUR		NORMAL WITH FUNCTIONAL MURMUR		TOTAL NORMALS		UNCLASSIFIED		CONGENITAL HEART DISEASE		POTENTIAL RHEUMALTIC HEART DISEASE		RHEUMATIC HEART DISEASE WITHOUT HISTORY OR RHEUMATIC FEVER		RHEUMATIC HEART DISEASE WITH HISTORY OF RHEUMATIC FEVER		TOTAL RHEUMATIC DISEASE	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
With positive family history of rheumatic fever	139	3.7	94	3.4	35	4.2	129	3.6	4	6.3	1	4.0	1	3.8	2	5.0	2	9.1	5	5.7
Without positive family history of rheumatic fever	3,651	96.3	2,685	96.6	800	95.8	3,485	96.4	59	93.7	24	96.0	25	96.2	38	95.0	20	90.9	83	94.3
Total	3,790	100.0	2,779	100.0	835	100.0	3,614	100.0	63	100.0	25	100.0	26	100.0	40	100.0	22	100.0	88	100.0

TABLE XI

SHOWING DISTRIBUTION AND PERCENTAGE BY RACE AND DIAGNOSIS
Total of 3,790 Cases, 1940 to 1941 Surveys (H)

RACE	TOTAL		NORMAL WITHOUT MURMUR		NORMAL WITH FAMILY HISTORY OF RHEUMATIC FEVER		NORMAL WITH FUNCTIONAL MURMUR		TOTAL NORMAL		CONGENITAL HEART DISEASE		POTENTIAL RHEUMATIC HEART DISEASE		RHEUMATIC HEART DISEASE WITHOUT HISTORY OF RHEUMATIC FEVER		RHEUMATIC HEART DISEASE WITH HISTORY OF RHEUMATIC FEVER		TOTAL RHEUMATIC DISEASE		UNCLASSIFIED	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
White	3,396	89.6	2,389	89.0	88	93.6	756	90.5	3,233	89.5	23	92.0	24	92.4	38	95.0	19	86.4	81	92.0	59	93.6
Indian	82	2.2	60	2.2	3	3.2	13	1.6	76	2.1+	-	-	1	3.8	1	2.5	2	9.1	4	4.6	2	3.2
Negro	20	0.5	17	0.6	-	-	3	0.4	20	.55	-	-	-	-	-	-	-	-	-	-	-	-
Mexican	246*	6.5	186	6.9	1	1.1	52	6.2	239	6.64	2	8.0	1	3.8	1	2.5	1	4.5	3	3.4	2	3.2
Filipino	1	0.0	1	0.1	-	-	-	-	1	.02	-	-	-	-	-	-	-	-	-	-	-	-
Oriental	6	0.2	4	0.1	-	-	2	0.2	6	.17	-	-	-	-	-	-	-	-	-	-	-	-
Unknown	39	1.0	28	1.1	2	2.1	9	1.1	39	1.1	-	-	-	-	-	-	-	-	-	-	-	-
Total	3,790	100.0	2,685	100.0	94	100.0	835	100.0	3,614	100.0	25	100.0	26	100.0	40	100.0	22	100.0	88	100.0	63	100.0

Two hundred nineteen of these cases were from Redlands and constituted 35.3 per cent of the total number examined in that city. In the remaining thirty-three Mexican children only one case of organic heart disease was found and a "rheumatic without history."

TABLE XIV

DISTRIBUTION AND PERCENTAGE OF CERTAIN SIGNS AND SYMPTOMS OF ORGANIC TROUBLES BY DIAGNOSTIC GROUP
Total of 3,790 Cases, 1940 to 1941 Surveys (H)

	TOTAL		NORMAL WITHOUT MURMUR		NORMAL WITH FAMILY HISTORY OF RHEUMATIC FEVER		NORMAL WITH FUNCTIONAL MURMUR		TOTAL NORMAL		UNCLASSIFIED		CONGENTAL HEART DISEASE		POTENTIAL RHEUMATIC HEART DISEASE		RHEUMATIC HEART DISEASE WITHOUT HISTORY OF RHEUMATIC FEVER		RHEUMATIC HEART DISEASE WITH HISTORY OF RHEUMATIC FEVER		TOTAL RHEUMATIC CASES	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Dyspnea	32	0.8	11	0.4	1	1.1	13	1.6	25	0.7	2	3.2	-	-	2	7.7	1	2.5	2	9.1	5	5.7
Fatigue	425	11.2	269	10.0	12	12.8	107	12.8	388	10.7	8	12.7	10	40.0	5	19.2	6	15.0	8	36.4	19	21.6
Palpitation	91	2.4	41	1.5	2	2.1	27	3.2	70	2.1	4	6.3	6	24.0	1	3.8	5	12.5	5	22.7	11	12.5
Sweats	66	1.7	31	1.2	1	1.1	21	2.5	53	1.46	2	3.2	2	8.0	1	3.8	4	10.0	4	18.2	9	10.2
Blue baby	24	0.6	8	0.3	1	1.1	9	1.1	18	0.5	2	3.2	2	8.0	-	-	-	-	2	9.1	2	2.3
Other cardiac signs and symptoms	75	2.0	30	1.1	1	1.1	25	3.0	56	1.5	5	7.9	7	28.0	1	3.8	1	2.5	5	22.7	7	8.0
None given	3,225	85.1	2,350	7.5	79	84.0	686	82.2	3,115	86.2	46	73.0	12	48.0	16	61.5	29	72.5	7	31.8	52	59.1
Total cases examined*	3,790	100.0	2,685	100.0	94	100.0	835	100.0	3,614	100.0	63	100.0	25	100.0	26	100.0	40	100.0	22	100.0	88	100.0

*The total of the vertical columns does not agree with the total number of children examined because of occurrence of multiple symptoms in certain patients.

TABLE XIII

EVALUATION OF HOUSING CONDITIONS, SHOWING DISTRIBUTION AND PERCENTAGE FOR EACH DIAGNOSTIC GROUP
Total of 3,790 Cases, 1940 to 1941 Surveys (H)

HOUSING EVALUATION	TOTAL		NORMAL WITHOUT MURMUR		NORMAL WITH FAMILY HISTORY OF RHEUMATIC FEVER		NORMAL WITH FUNCTIONAL MURMUR		TOTAL NORMAL		UNCLASSIFIED		CONGENITAL HEART DISEASE		POTENTIAL RHEUMATIC HEART DISEASE		RHEUMATIC HEART DISEASE WITHOUT HISTORY		RHEUMATIC HEART DISEASE WITH HISTORY		TOTAL RHEUMATIC	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Poor	736	19.4	529	19.7	20	21.3	157	18.8	706	19.5	8	12.7	6	24.0	3	11.5	8	20.0	5	22.7	16	18.2
Fair	1,484	39.2	994	37.0	42	44.7	354	42.4	1,390	38.5	35	55.6	10	40.0	15	57.7	20	50.0	14	63.6	49	55.7
Good	1,570	41.4	1,162	43.3	32	34.0	324	38.8	1,518	42.0	20	31.7	9	36.0	8	30.8	12	30.0	3	13.7	23	26.1
Total	3,790	100.0	2,685	100.0	94	100.0	835	100.0	3,614	100.0	63	100.0	25	100.0	26	100.0	40	100.0	22	100.0	88	100.0
1 or less per room	2,659	70.2	1,881	70.1	57	60.6	595	71.2	2,533	70.+	51	81.0	18	72.0	20	77.0	28	70.0	9	40.9	57	64.8
More than 1, less than 1½	588	15.5	414	15.4	24	25.6	120	14.4	558	15.4	6	9.5	3	12.0	3	11.5	10	25.0	8	36.4	21	23.9
1½ or more per room	543	14.3	390	14.5	13	13.8	120	14.4	523	14.5	6	9.5	4	16.0	3	11.5	2	5.0	5	22.7	10	11.3

TABLE XV

SHOWING DISTRIBUTION AND PERCENTAGE BY AGE AND DIAGNOSIS
Total of 3,790 Cases of 1940 to 1941 Surveys (H)

AGE (YR.)	TOTAL		NORMAL WITHOUT MURMUR		NORMAL WITH FAMILY HISTORY OF RHEUMATIC FEVER		NORMAL WITH FUNCTIONAL MURMUR		TOTAL NORMAL		UNCLASSIFIED		CONGENITAL HEART DISEASE		POTENTIAL RHEUMATIC HEART DISEASE		RHEUMATIC HEART DISEASE WITHOUT HISTORY OF RHEUMATIC FEVER		RHEUMATIC HEART DISEASE WITH HISTORY OF RHEUMATIC FEVER		TOTAL RHEUMATIC CASES		PERCENTAGE OF EACH AGE GROUP			
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	TOTAL RHEUMATIC DISEASE	RHEUMATIC HEART DISEASE	CONGENITAL HEART DISEASE	TOTAL HEART DISEASE
0 to 4	21	0.6	14	0.5	1	1.1	4	0.4	19	5.0	-	-	2	8.0	-	-	-	-	-	-	-	-	-	-	9.5	9.5
5 to 9	1,550	40.9	1,099	40.9	43	45.7	343	41.1	1,485	41.5	31	49.2	14	56.0	7	26.9	9	22.5	4	18.2	20	22.7	2.9-	0.83	0.91	1.74
10 to 14	1,520	40.1	1,050	39.1	43	45.7	343	41.1	1,436	40.4	26	41.3	7	28.0	14	53.9	24	60.0	13	59.1	51	58.0	3.3	2.43	0.46-	2.89
15 to 19	696	18.4	519	19.3	7	7.5	145	17.4	671	18.5	6	9.5	2	8.0	5	19.2	7	17.5	5	22.7	17	19.3	2.4	1.71	0.29-	2.0
20+	2	0.0	2	0.1	-	-	-	-	2	0.05	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Unknown	1	0.0	1	0.1	-	-	-	-	1	0.03	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Total	3,790	100.0	2,685	100.0	94	100.0	835	100.0	3,614	100.0	63	100.0	25	100.0	26	100.0	40	100.0	22	100.0	88	100.0	2.32	1.63	0.66	2.29

nizable concentration of the rheumatic population in houses evaluated as fair, 55.7 per cent, as compared to 38.5 per cent of the normal subjects. This is not shown in poor housing, although, when poor and fair housing are consolidated and contrasted to good housing, there is a material difference, i.e., 74 per cent in rheumatics and 58 per cent in normals. A similar situation obtains in the apparent effect of the crowding element of housing, but is less evident than in the general housing classification, i.e., 35.2 per cent of the rheumatic group and 30 per cent of the normal population were living in houses with more than one person per room.

Table XIV summarizes the history of certain common cardiac signs and symptoms. More extensive tables of phenomena associated with heart disease and rheumatism were prepared, but are not presented because the data contained did not seem significant. With the exception of fatigue, the source of which is manifold, no other signs or symptoms were reported in consequential number among normal children.

Dyspnea, fatigue, palpitation, and excessive sweating were relatively common in the rheumatic population. Unusual dyspnea on exertion may have been due to poor training after confinement to bed or limited activity, rather than heart failure. This would explain its relative infrequency in "rheumatic heart disease without history," as compared to those patients with and without heart disease but with a history of rheumatic fever. Palpitation was relatively frequent only among children with heart disease. The occurrence of two blue babies at birth, reported as rheumatic heart disease, only indicates that this historical finding is often unreliable.

Table XV presents the age distribution of the children studied. As would be expected, and as in the San Francisco[17] and other surveys, congenital heart lesions are more common than rheumatic valvulitis prior to the age of 9 years. It is recognized through several surveys that the greatest number of children with rheumatic disease have their initial attack between 10 and 16 years of age. One would assume that more children would be found with evidence of rheumatic heart disease over this age than under it. Although this was the situation in a previous San Francisco study, it is not uniformly the case, nor was it found in the current study.

Presenting the data in a different way than in the table, it is found that, from the ages of 5 through 9 years, 2.9 per cent of the population had rheumatic disease and 0.8+ per cent had valvulitis. From the ages of 10 through 14 years, the incidences were 3.3 per cent and 2.4 per cent, respectively, and from 15 through 19 years, 3.4 per cent and 1.7 per cent. The fact that there is a lower incidence of rheumatic heart disease in late youth has been frequently reported. The accepted explanation is that signs of valvulitis are evanescent, and are transiently lost in the adolescent and postadolescent period.

Table XVI does not show a high incidence of rheumatic disease in the lower dietary brackets. The diet history for special elements was

not obtained except for vitamin C and carbohydrate content. Rinehart and Mettier, in 1934,[39] and later, with other collaborators,[40] presented evidence that rheumatic fever was a result of latent scurvy with superimposed infection. This view was partially corroborated by Stimson, Hedley, and Rose,[41] but Sendroy and Schultz[42] and Perry[43] failed to find confirmatory evidence of any specific relation of vitamin C deficiency and rheumatic fever.

In the Redlands survey (H), all five rheumatic children had been using adequate amounts of citrus fruits (groups +++ and ++++). However, in Table XVI the rheumatic population seems to be concentrated in lower brackets of vitamin C intake. This may suggest a contributory, rather than a required, causative relation of vitamin C intake and rheumatic fever.

The carbohydrate study was largely to ascertain the relation to dental caries. Only in the ++++ bracket was there an apparent correlation. There was no greater incidence of dental caries in rheumatic than in normal children, 15.9 per cent and 16.3 per cent, respectively.

There was no correlation of rheumatic disease with malnutrition, or with a history of frequent throat infections or of appreciable cervical lymphadenopathy.

Of rheumatic children, 11.4 per cent had had scarlet fever, as contrasted to 8.9 per cent of normal children, but no data were available as to the interval between the scarlet fever and the rheumatic fever. These figures, therefore, are not significant.

Of the rheumatic children, 41 per cent had had their tonsils and adenoids removed, as contrasted with 36 per cent of normal children, but there was no history available on the development or exacerbation of rheumatic fever in relation to the time the tonsillectomy was performed. These figures are of no material significance.

According to the criteria of hypertension as stated above, the incidence was 3.4 per cent in the entire group. The incidence in rheumatic children was 8 per cent, which is of interest in view of the association of hypertension with rheumatic heart disease later in life. On the contrary, it is believed that the hypertension discovered in children is probably transient and due to psychic influences, which well may be more prominent in the rheumatic child.

Although the number of functional murmurs has been included in all the tables presented, there has been no correlation with any factors discussed in this survey. Even the age groupings (5 to 9 years; 10 to 14 years; 15 to 19 years) failed to show any concentration of such cases.

CONCLUSIONS

1. The school populations of three California communities with markedly different climates were surveyed for the incidence of heart disease, rheumatic fever, functional heart murmurs, and hypertension

TABLE XVI

DISTRIBUTION AND PERCENTAGE OF DIAGNOSTIC GROUPS ACCORDING TO FOOD CONSUMPTION AND INCIDENCE OF MARKED DENTAL CARIES
3,790 Cases of 1940 to 1941 Survey (H)

		TOTAL		TOTAL NORMAL		UN-CLASSIFIED		CONGENITAL HEART DISEASE		POTENTIAL RHEUMATIC HEART DISEASE		RHEUMATIC HEART DISEASE WITHOUT HISTORY OF RHEUMATIC FEVER		RHEUMATIC HEART DISEASE WITH HISTORY OF RHEUMATIC FEVER		TOTAL RHEUMATIC DISEASE		DENTAL CARIES	
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
General diet	+	536	14.2	512	14.2	8	12.7	3	12.0	2	7.7	6	15.0	5	22.7	13	14.8	-	-
	++	871	23.0	829	22.8+	15	23.8	11	44.0	6	23.1	6	15.0	4	18.2	16	18.2	-	-
	+++	1,335	35.2	1,266	35.0+	26	41.3	8	32.0	10	38.4	14	35.0	11	50.0	35	39.8	-	-
	++++	1,048	27.6	1,007	28.1	14	22.2	3	12.0	8	30.8	14	35.0	2	9.1	24	27.2	-	-
	Total	3,790	100.0	3,614	100.0	63	100.0	25	100.0	26	100.0	40	100.0	22	100.0	88	100.0	-	-
Vitamin C	+	138	3.6	123	3.4	9	14.3	-	-	1	3.8	3	7.5	2	9.1	6	6.8	-	-
	++	298	7.9	277	7.6	6	9.5	4	16.0	2	7.7	5	12.5	4	18.1	11	12.5	-	-
	+++	1,179	31.1	1,108	30.6	28	44.4	11	44.0	5	19.2	19	47.5	8	36.4	32	36.4	-	-
	++++	2,175	57.4	2,106	58.5	20	31.8	10	40.0	18	69.3	13	32.5	8	36.4	39	44.3	-	-
	Total	3,790	100.0	3,614	100.0	63	100.0	25	100.0	26	100.0	40	100.0	22	100.0	88	100.0	-	-
Carbohydrates	+	55	1.4	53	1.5	2	3.2	-	-	-	-	-	-	-	-	-	-	8	1.3
	++	771	20.3	738	20.4	11	17.4	6	24.0	2	7.7	11	27.5	3	13.6	16	18.2	102	16.7
	+++	1,712	45.2	1,611	44.6	41	65.1	9	36.0	18	69.3	18	45.0	15	68.2	51	58.0	253	41.5
	++++	867	22.9	840	23.0	7	11.1	6	24.0	5	19.2	5	12.5	4	18.2	14	15.9	129	21.1
	+++++	385	10.2	372	10.6	2	3.2	4	16.0	1	3.8	6	15.0	-	-	7	7.9	118	19.4
	Total	3,790	100.0	3,614	100.0	63	100.0	25	100.0	26	100.0	40	100.0	22	100.0	88	100.0	610	100.0
Dental caries		610	100.0	580	95.0	9	1.5	7	1.1	4	0.7	7	1.1	3	0.5	14	2.3	610	100.0

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by a single skilled physician, using a uniform technique and uniform criteria of diagnosis. One of these communities was previously surveyed by a second physician, who used approximately the same technique and criteria.

2. Rheumatic fever and rheumatic heart disease occur in the warm, dry climate of Redlands in a degree comparable to cities with mild, temperate climates, such as Cincinnati and San Francisco.

3. Susanville, a mountain community with average humidity and precipitation, but with wide extremes of average winter and summer temperatures, presented a high incidence of rheumatic fever and rheumatic heart disease, comparable to the incidence in the northeastern United States or Great Britain.

4. Eureka, with a uniformly cool climate and high precipitation, presented an unusually high incidence of rheumatic disease, especially of valvulitis.

5. Congenital heart lesions were found in greater frequency than in all previous surveys except those reported previously from other California communities.

6. Children with rheumatic valvulitis gave fewer past histories and family histories of rheumatic fever than in other reports.

7. Certain statistical relations seem to exist between rheumatic disease and age, sex, race, and housing. Questionable relations exist to diet and to a history of scarlet fever. No definite relation of functional murmurs to any physical, symptomatic, or environmental influences, such as age, shape of chest, or nutritional state, was found.

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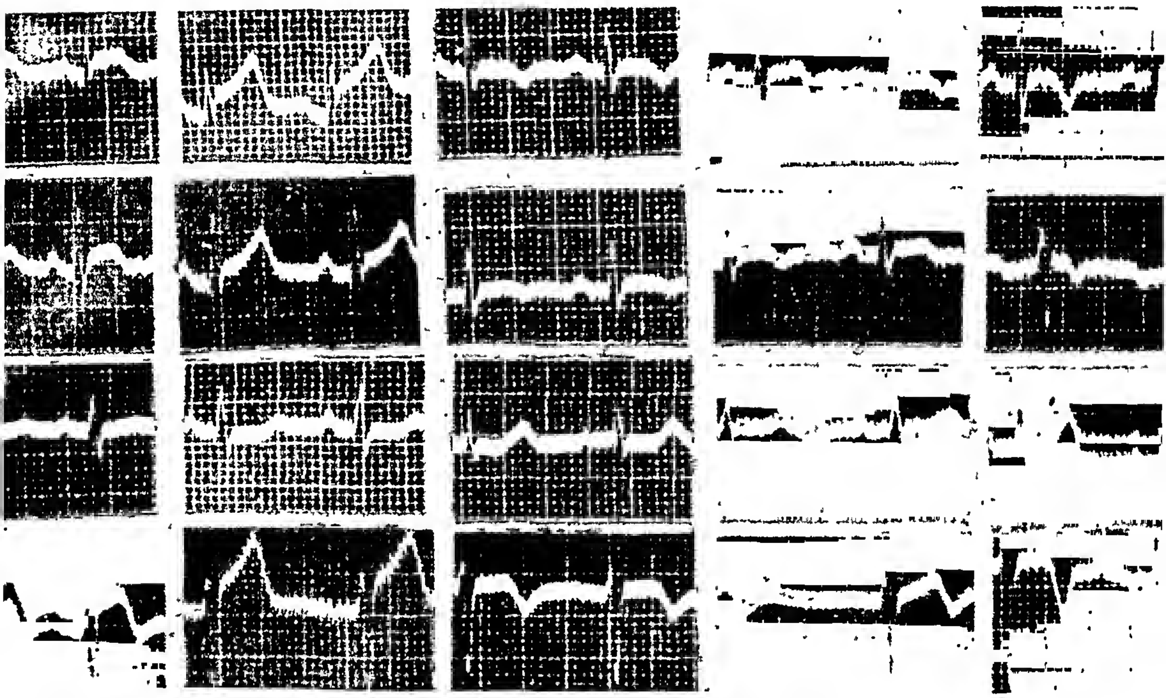
100 per cent humidity. The temperature of the patient could be controlled easily by varying the intensity of the heat and by applying ice water to the head. On removal from the cabinet the blood pressure was taken and varied from 70/50 to 120/75. On return to the ward after the temperature had become normal, 1,000 c.c. of 5 per cent glucose in normal saline solution were given intravenously. The patient remained in bed thirty-six hours. In the cases of coronary occlusion this routine was followed, and the patients completed the full course of fever with no difficulty or unusual discomfort.



Oct. 27 Oct. 28 Oct. 29 Nov. 8 Nov. 22

Fig. 1.—Case 1. Fever therapy on Oct. 26, 1943. October 27: Lead I. The QRS complex is of low amplitude. The S-T segment is slightly elevated, and ends in a biphasic T wave. Lead II. The appearance of the S-T segment and T wave is similar in this lead. Lead III: The T wave is upright. Lead IV: There is almost complete absence of the R wave. The S-T segment is elevated and ends in a biphasic T wave. October 28: The S-T segments in Leads I, II, and IV are elevated. The T waves in these leads are large and upright. The S-T segment in Lead III is slightly depressed, and the T wave is biphasic. October 29: The T waves are now definitely inverted in Leads I, II, and IV. November 8: The S-T segments are still arched; the T waves are inverted in Leads I and II, and biphasic in Lead IV. November 22: The T waves are now deeply inverted in Leads I, II, and IV.

Impression.—The progressive changes in these records are typical of those which occur after occlusion of the anterior descending branch of the left coronary artery. In this case the T waves were still abnormal ten weeks after the onset of the illness.

CASE REPORTS

Case 1.—This 24-year-old patient had gonococcal urethritis for which he was treated for four weeks prior to admission to this hospital with sulfathiazole and sulfadiazine. He received routine sulfonamide therapy here, with no improvement in his gonorrhea. Physical examination showed a normal cardiovascular system, with a blood pressure of 120/65. A roentgenogram of the heart was normal, but no electrocardiogram was taken prior to fever therapy. During the treatment

CORONARY OCCLUSION AFTER FEVER THERAPY FOR SULFONAMIDE-RESISTANT GONORRHEAL URETHRITIS

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FEVER therapy has been used in the treatment of eighty-five patients in a General Hospital. The electrocardiograms of three of these patients showed progressive changes typical of coronary occlusion of the anterior type. The patients were young adult males who had no disease other than chronic gonococcal urethritis which was resistant to sulfonamide therapy. Coronary occlusion as a complication of fever therapy has been observed rarely,[1] and the effects of such an occurence on persons of this age who were previously in excellent health is of considerable interest.

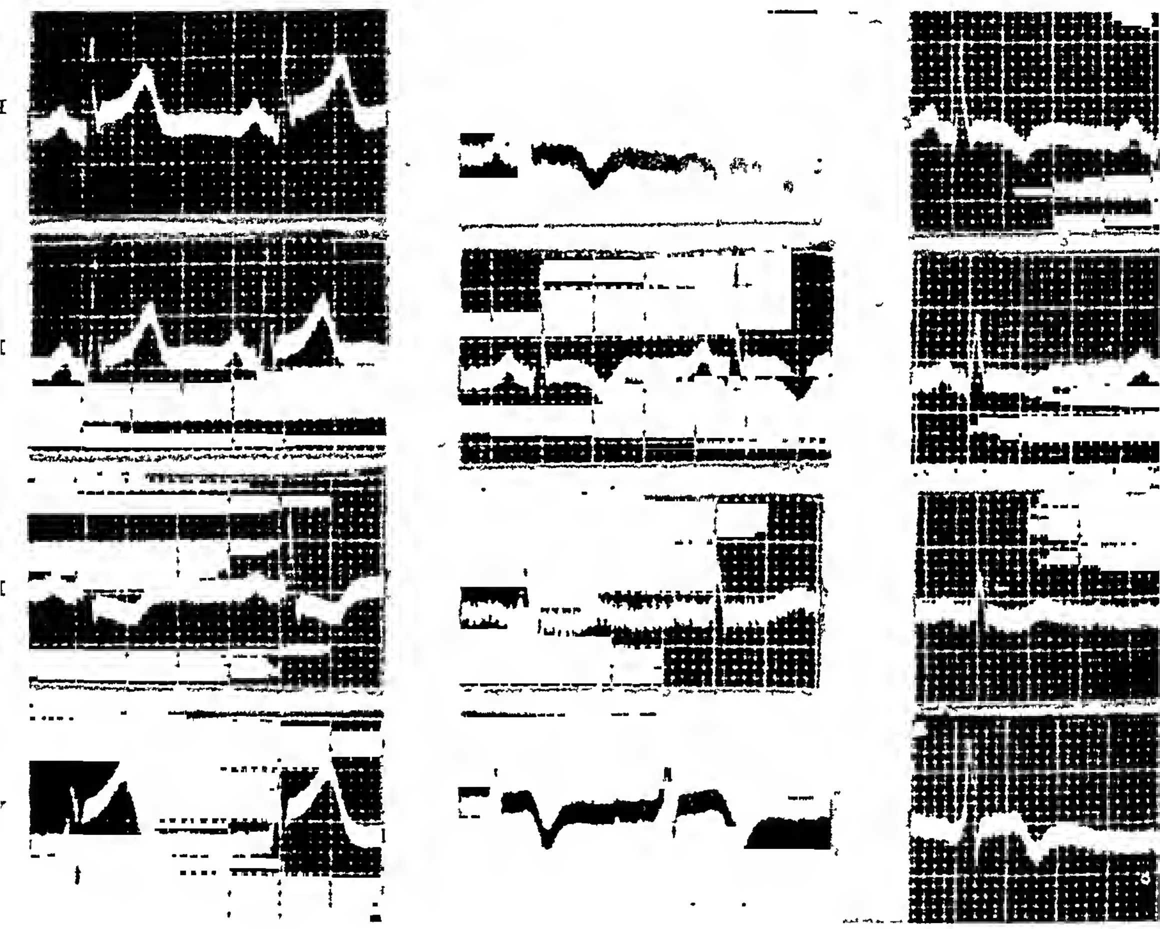
Fever therapy has been used in this hospital to treat neurosyphilis and nonspecific iridocyclitis, but for the most part in treating sulfonamide-resistant gonorrhea. A full course of therapy consisted of maintaining a rectal temperature at 106 to 107° F. for five to seven hours. Gonorrhea was considered resistant to sulfonamide therapy after the administration of 35 Gm. of sulfathiazole in five days, followed for five more days by the same amount of sulfadiazine. This was in addition to sulfonamide therapy which was given in many cases prior to the admission of the patient to this hospital.

Prior to the fever therapy the sulfonamide was discontinued for a period of one week. On the day before the hyperpyrexia, 10 Gm. of sodium chloride and 3,000 c.c. of water were given by mouth between noon and bedtime. The patient was encouraged to take a full diet, with 10 Gm. of brewer's yeast in addition. At bedtime 3 Gm. of sulfathiazole were administered by mouth, and in the morning an additional 2 Gm. were given. Just before entry into the cabinet, 15 c.c. of paraldehyde were given orally, and further sedation during the course of the treatment consisted of 8 mg. of morphine in the first hour, followed several hours later by 0.3 mg. of scopolamine. For the most part the patients were quiet and cooperative during the treatment. The average time taken for the rectal temperature to reach 106° F. was one and a half hours. As the temperature varied between 106 and 107,° the pulse rate ranged from 140 to 160 per minute. Iced physiologic saline was given by mouth throughout the treatment, and the average intake was 1,500 to 2,000 cubic centimeters. The temperature elevation was maintained by means of radiant heat supplied by ten 100-watt electric light bulbs in an atmosphere approaching

Received for publication April 26, 1944.

completely subsided and he felt quite normal. His blood pressure remained at 85/50. For two days after the treatment he had fever, with a temperature up to 102° F., and for one week there were a moderate leucocytosis and acceleration of the sedimentation rate to 30 mm. per hour. His blood pressure did not return to normal for ten days. The electrocardiographic changes are described in Fig. 1.

Case 2.—Before admission to the hospital this 19-year-old patient had received "large doses" of sulfonamides for a fifteen-day period.



Dec. 1 Dec. 3 Dec. 16

Fig. 3.—Case 3. Fever therapy on Nov. 30, 1943. December 1. There is elevation of the S-T take-off in Leads I and II, and to a greater extent in the chest lead. Slight depression of this segment in Lead III, ending in a biphasic T wave. The QRS complex in Lead IV is of low amplitude, and the R wave is a little slurred. December 3. In this record the T wave is deeply inverted in Leads I, II, and III. The QRS complex is still very small in Lead IV, and the R wave is slurred. December 16. There is still inversion of $T_{1, 2 \text{ and } 4}$. T_3 has a tendency to be biphasic. The R wave in Lead IV is now much larger.

Impression.—The progressive changes in these records are indicative of coronary occlusion, probably anterior in type. A record taken Jan. 30, 1944, still showed inversion of T_4 but the other T waves were upright.

Prior to the fever treatment he received 35 Gm. of sulfathiazole in five days, followed during the next five-day period by 35 Gm. of sulfadiazine. There was no lessening of the urethral discharge, and no toxic manifestations of the drug therapy were noted. This patient was given the routine preparation for fever therapy. On physical examination his heart and lungs were normal, and his blood pressure was 115/75.

his pulse was regular and of good quality, and at no time did the rate exceed 160 beats per minute. During the period in the cabinet he took 2,400 c.c. of physiologic saline by mouth, and was quiet and cooperative. On removal from the cabinet his blood pressure was 70/50. When his temperature returned to normal his pulse rate was 86, and, after the intravenous treatment, his blood pressure rose to 100/60.

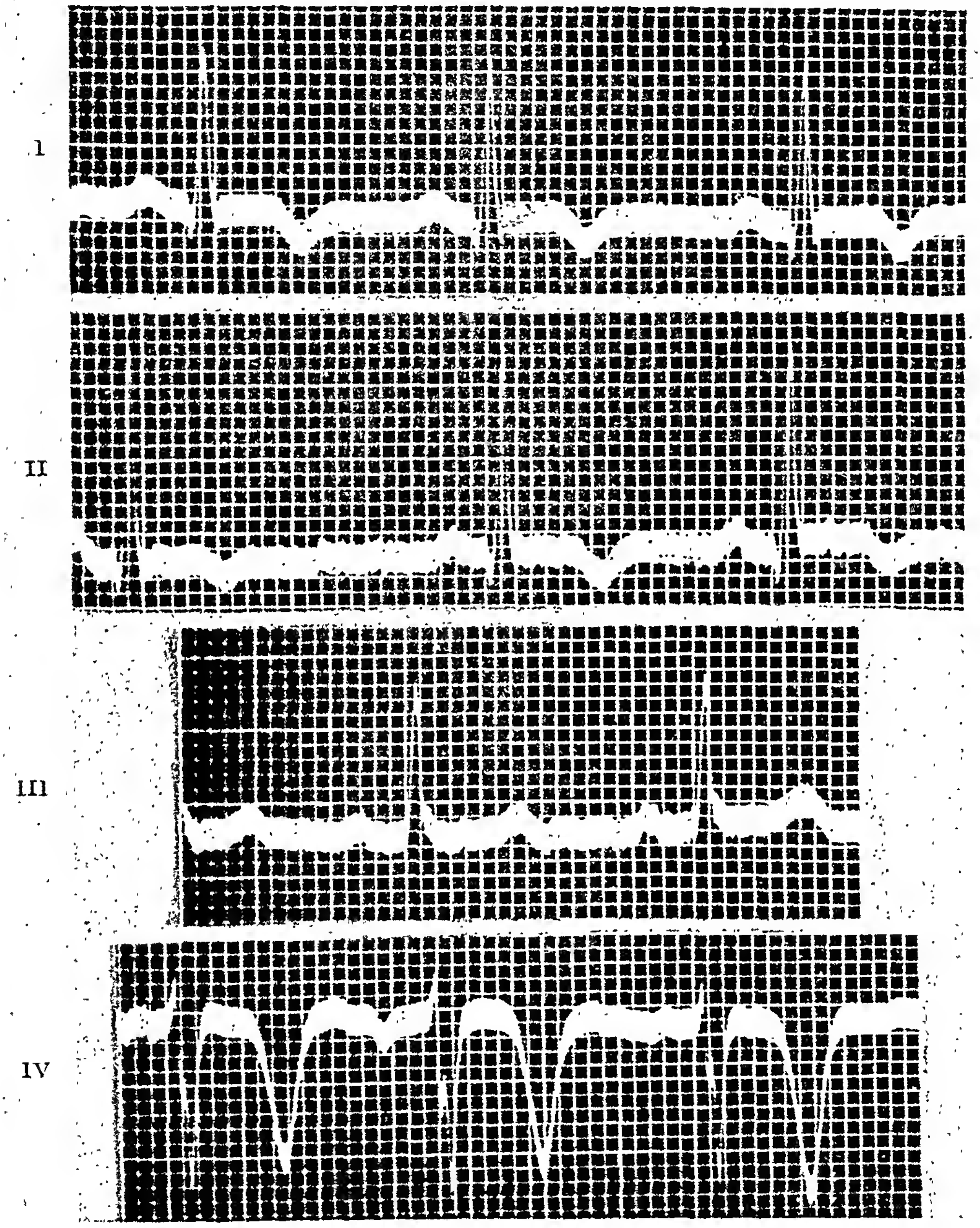


Fig. 2.—Case 2. Fever therapy on Nov. 19, 1943. December 23: Lead I: The S-T segment is arched, and ends in an inverted T wave. Lead II: The S-T segment has the same appearance as in Lead I, but the T wave is not so deeply inverted. Lead III: essentially normal in appearance. Lead IV: An auricular premature beat is visible. The R wave is almost entirely absent, and the T wave is very deeply inverted.

Impression.—These changes are typical of those which occur with coronary occlusion of the anterior type. An electrocardiogram taken on March 5, 1944, showed normal T waves, but the R wave in Lead IV was still very small.

The following morning he complained of a moderately severe, oppressive feeling beneath the sternum. He appeared rather apprehensive and pale, but was quiet. His blood pressure was 70/40, and his pulse rate, 84. The heart sounds were distant. Four hours later his symptoms had

These facts, coupled with the drastic nature of the therapy, make it reasonable to assume that this complication is more widespread than has been previously suspected, and that electrocardiograms should be taken routinely before and during the twenty-four- to seventy-two-hour period after fever therapy. The development of this type of cardiac lesion as an aftermath of fever treatment has been reported but rarely. In the three cases described here, the progressive changes in the electrocardiogram were typical of occlusion of a coronary artery, and they persisted for the entire time the patients were under observation, which varied from six to ten weeks.

Trautman[2] has reported the complications in a series of 6,881 treatments with therapeutic hyperpyrexia. The blood pressure fell to 80 mm. Hg, systolic, or below, in 8.5 per cent of the patients. It seems possible that, among this group, cases of the type described in this communication might have been discovered if electrocardiograms had been taken.

After these cases were observed, records were made routinely before and for three days after therapeutic hyperpyrexia in a series of fifteen cases. In two cases, other than those reported, the electrocardiograms showed a coronary type of S-T segment and T-wave change within twenty-four hours which persisted for several days, but then reverted to normal. Neither patient had any complaints referable to the cardiovascular system. In several others, a transient cardiac arrhythmia was observed in additon to minor changes in the S-T segments and T waves; this was of short duration (Fig. 4).

In view of the typical electrocardiographic abnormalities in these three cases, with progressive changes persisting after five to ten weeks, the diagnosis of coronary occlusion seems quite conclusive. The pathogenesis of the occlusion is not clear. Miller and Woods[3] analyzed twelve cases of coronary thrombosis occurring in patients between the ages of 20 and 30 years. Ten of their patients were men and two were women. There was no predilection for race or occupation. Four died in the first attack. There was a history of rheumatic fever in one, and in none was syphilis the cause. Atheroma or atherosclerosis was found in all four cases in which there were adequate autopsy data. The anterior descending branch of the left coronary artery was most frequently the site of thrombosis.

It is possible that in the cases of the present series an atheromatous nidus existed, and that changes in fluid and electrolyte balance or in the coagulability of the blood as a result of the prolonged high temperature might have been the precipitating factor. It is of interest, in view of the autopsy observations noted above, that in all of these cases the electrocardiograms pointed to the anterior descending branch of the left coronary artery as the seat of the thrombosis. The patients in the present series recovered promptly from their symptoms, but continued

During fever therapy, his temperature rose from normal to 106° F. in eighty-eight minutes. His pulse was regular and of good quality throughout the treatment, with a rate between 140 and 160 per minute. The fluid intake during his stay in the cabinet was 1,800 c.c. of physiologic saline orally. One hundred fifty minutes after removal from the cabinet his blood pressure was 110/50, and his pulse rate was 116 per minute. The pulse rate soon fell to 86 per minute. The following day he felt normal, and was soon discharged from the hospital, cured of his urethral discharge. Five weeks later he was readmitted to another hospital for a second gonorrheal infection, and an electrocardiogram was made preparatory to further fever therapy. Although the patient felt perfectly well, and although physical examination was negative and his blood pressure was perfectly normal, the electrocardiogram showed the typical T-wave changes which follow occlusion of the anterior descending branch of the left coronary artery (Fig. 2).

CASE 3.—This 25-year-old patient was admitted to the hospital because of gonococcal urethritis. He received sulfathiazale and sulfadiazine according to the usual routine, with no improvement. This was followed one week later by fever therapy, with a temperature of about 105.6° F. for eight hours. He took 1,500 c.c. of physiologic saline by mouth; his pulse rate remained below 160 per minute, and he did not become restless or have any complaints. The next morning, about sixteen hours after removal from the cabinet, he complained of a numb feeling in both arms and a sensation of tightness and aching pain beneath the upper part of the sternum. He was fairly apprehensive, but his breathing was quiet and he was not cyanotic or dyspneic. The lungs were normal. The heart was not enlarged, the sounds were of quite good quality, and no murmurs were audible. The blood pressure, which had been 120/60 before treatment, was now 106/70. He appeared well hydrated, and the hematocrit reading was normal. An electrocardiogram taken at this time showed changes typical of coronary occlusion of the anterior type (Fig. 3). There was a slight rise in temperature, the leucocyte count rose to 13,000 per c. mm., and the sedimentation rate was 14 mm. per hour. Two days later he still complained of pain, and at that time had tenderness in the region of the left trapezius muscle. The blood pressure had risen to normal, and examination of the heart revealed no abnormalities. At no time was he acutely ill. His urethral discharge disappeared after the fever therapy and did not return. Recovery was uneventful. The electrocardiogram showed the progressive changes characteristic of occlusion of the anterior descending branch of the left coronary artery. Residual changes were still present in records made eight weeks after the onset of the illness.

DISCUSSION

Three patients developed electrocardiographic changes typical of occlusion of a coronary artery after fever therapy for sulfonamide-resistant gonococcal urethritis. All of these patients were healthy young soldiers; their ages were 24, 19, and 25 years, respectively. In none of these cases was there any reason to suspect any abnormality of the cardiovascular system prior to the treatment. In one case there were never any symptoms referable to the heart, and in the other two they were relatively mild and the patients were never seriously ill.

ent frequency and the possible effect on the future health of the patient of this complication, it is recommended that penicillin be used in the treatment of sulfonamide-resistant gonococcal infections whenever it is possible.

SUMMARY

1. Three cases of coronary occlusion occurred after the administration of therapeutic hyperpyrexia for sulfonamide-resistant gonococcal urethritis.

2. All of the patients were young adult males and had no pre-existing disease of the cardiovascular system. In no instance was the patient critically ill.

3. Electrocardiograms in each case showed progressive changes similar to those which occur with occlusion of the anterior descending branch of the left coronary artery. In two cases, definite T-wave changes were still present eight and ten weeks after the onset. In the third, a record made fifteen weeks after the therapeutic hyperpyrexia revealed normal T waves.

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to have abnormal electrocardiograms for many weeks after the onset, so that the effect on the state of the cardiovascular system in the future cannot be predicted. The serious nature of this complication makes it desirable to take electrocardiograms routinely before and during the twenty-four- to seventy-two-hour period after fever treatment. Only in this manner can those cases in which there are few or no symptoms

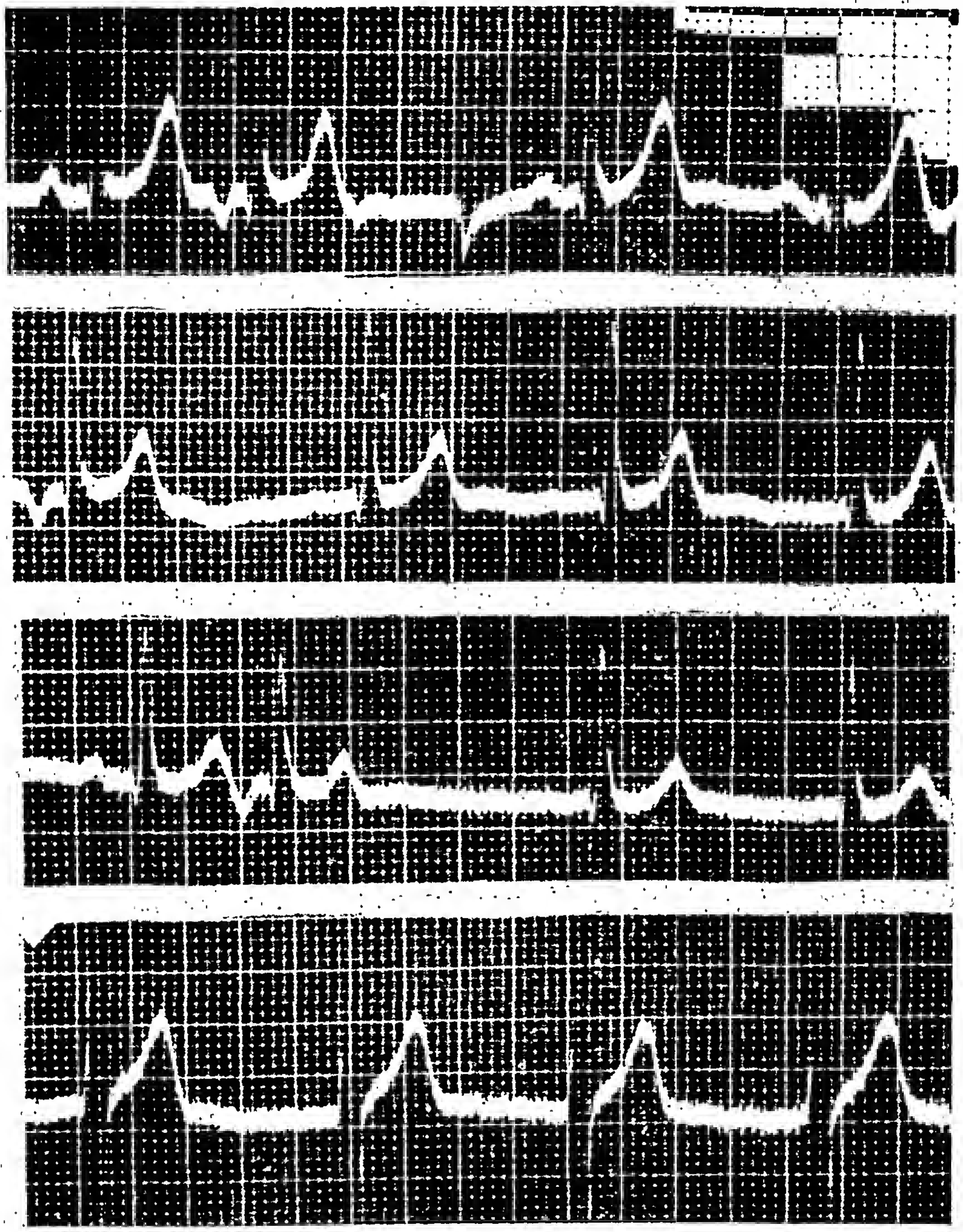
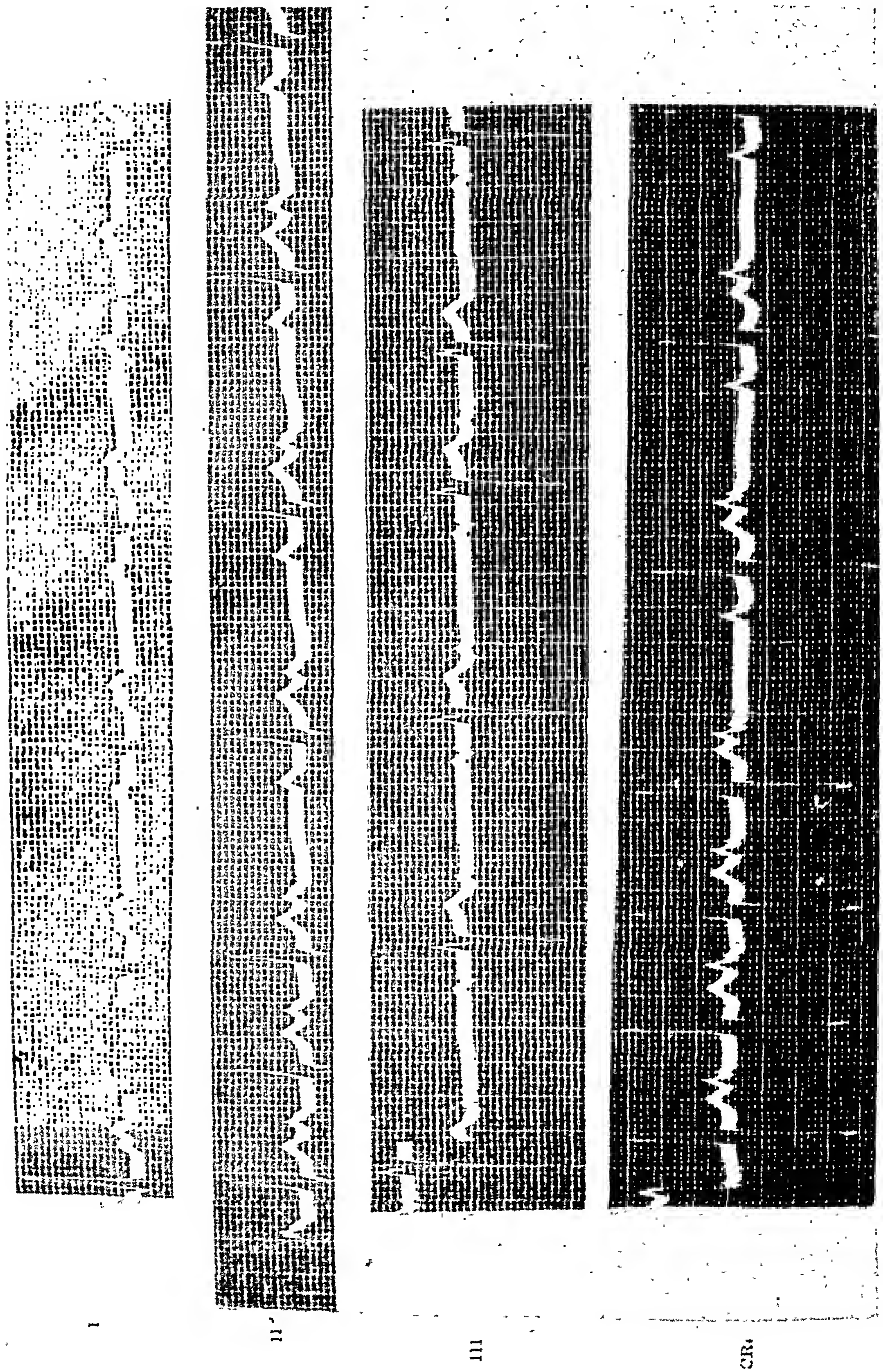


Fig. 4.—This record, taken forty-eight hours after fever therapy, shows one type of cardiac arrhythmia which may occur. There were numerous auricular premature beats, some of which were followed by short periods of A-V nodal rhythm. This persisted for four days after termination of the therapeutic hyperpyrexia. Leads I to IV, from above downward.

be recognized and proper therapy instituted. It is of interest that one patient in this series never had any cardiac symptoms, was discharged without any restriction of activity, and five weeks later had a routine electrocardiogram which revealed the diagnosis. In view of the appar-


I
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PERIODIC CHANGES IN THE FORM OF THE P WAVES IN PARTIAL HEART BLOCK

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NEW YORK, N. Y.

IN EXPERIMENTAL[1] and clinical heart block[2, 3] a peculiar disturbance of the auricular rhythm may be observed; it consists of a prolongation of one or two of the auricular cycles which follow ventricular contractions. This phenomenon was attributed to rhythmic variation of vagal tonus.[1] Reflex inhibition of the heart by stimulation of the pressor nerves in the aorta and carotid sinus can wax and wane within one single cycle.[4, 5, 6] These periodic changes in auricular rate are not rare.

The phenomenon was markedly developed in nine out of fifteen cases of complete heart block; in three other cases in the same series it was inconstant and less distinct, but in only three patients was it absent.[7] It is very common in 2:1 block. Here the auricular periods during which a ventricular contraction occurs are shorter than the others, and the P waves which follow a ventricular contraction seem premature. The differentiation from auricular extrasystoles is therefore necessary and usually easy. The form of the P waves remains constant in cases of heart block, whereas the premature P wave in auricular extrasystoles usually shows a different form.

Auricular extrasystoles which originate in the sinus node have P waves of the same form as those of the sinus beats; accordingly, the picture is similar to 2:1 block with alternating length of the auricular period, but such extrasystoles are very rare. In most cases of partial heart block exercise produces a change in the type of the block, and this would aid in differential diagnosis.

In heart block, however, periodic changes in the form of the P waves may occur; they are independent of the disturbance of rate, but sometimes they are combined with it.

The electrocardiogram shown in Fig. 1 was obtained from an 18-year-old patient with rheumatic fever. The P waves are abnormally wide and split, and there is left axis deviation with some slurring of the QRS complexes. The tracings show 2:1 block, with delayed auriculoventricular conduction interchanging with periodically dropped beats. The patient had not received digitalis. It is clear that those P waves which appear after a long ventricular diastole have a different form than those which appear soon after a T wave. The change is present in all leads and is most marked in Lead II. In this tracing the P waves

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Received for publication April 26, 1944.

which appear after a longer ventricular diastole are sharper and do not show notching in the downstroke, as do the other P waves. During the series of conducted beats the form of the P waves is constant. The change, however, is always present during the 2:1 block.

The auricular cycle which includes a ventricular contraction measures 0.64 second, whereas the others measure 0.68 to 0.70 second. The P waves of abnormal configuration appear, therefore, to be slightly premature.

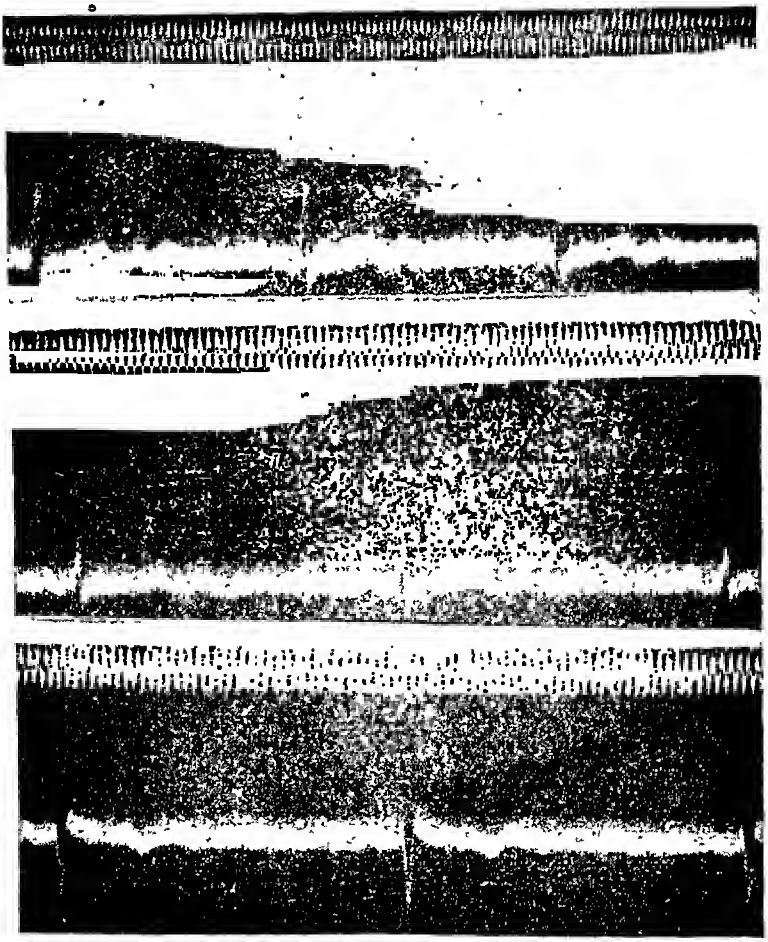

Fig. 3.—Changes in the *P* waves and 2:1 block.

Fig. 2 was obtained from a 48-year-old patient with rheumatic aortic insufficiency during a recurrence of his rheumatic fever (Lead CR_4). The patient had not received digitalis. The electrocardiogram shows periodically dropped beats (Wenckebach's periods). In this tracing, again, those P waves which follow a ventricular complex rather closely have a different form than the others. They are low and more split. The auricular rate is regular.

Fig. 3 shows the three limb leads of an electrocardiogram obtained from a 65-year-old patient with coronary sclerosis and angina pectoris. There is a 2:1 block, and a deep Q wave is visible in Lead III. In

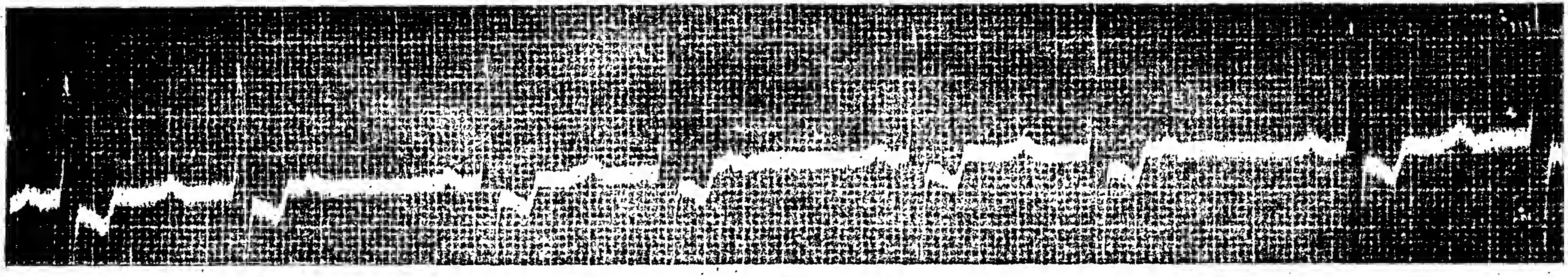

Fig. 2.—Periodically dropped beats with changes in the form of the P waves (CR_4).

Changes in the form of the P waves in partial or complete heart block are known to occur. The disturbance, however, is always visible for a series of beats, and does not concern exclusively those P waves which come early after a QRS complex. It is independent of ventricular activity, and is due to the fact that the disease which causes the heart block (diphtheria, coronary sclerosis) also involves the auricles and causes a shift of the pacemaker or a disturbance of intra-auricular conduction. The changes in the form of the P waves mentioned in this paper have not—as far as we can ascertain—been described before.

In those cases in which the alternation in the form of the P waves is combined with an alternation in the length of the auricular periods, confusion with auricular extrasystoles is easily possible. In all five cases, analysis of long tracings or exercise tests permitted one to exclude the presence of auricular extrasystoles.

In the first two cases (Figs. 1 and 2) the disturbance persisted as long as the partial heart block lasted, that is, for two and four days, respectively. In the other three cases no follow-up study was possible.

An explanation of this disturbance which comes to mind first is that there is superimposition of a U wave on those P waves which appear early in diastole and follow the T waves at an appropriate distance. It is known that, under some conditions, for instance in tachycardias, this summation may alter the form of the P waves, and this mechanism may play a role in some of the tracings reported. A study of other tracings, however, like that of Fig. 2, shows that the periodic alteration of the form of the P waves appears independent of U waves; the first, third, and fifth QRS complexes of this tracing show this clearly. The T waves of these QRS complexes are not followed by a U wave. Therefore, those abnormal P waves which appear a short distance after the T wave are not altered by summation with a U wave. Although U waves may be inverted, they are not sharp and peaked like the waves following the T waves in Lead III of Fig. 3.

Sometimes abnormal and premature P waves follow the QRS complex at a short interval in complete heart block. Originally they were explained as a result of mechanical irritation of abnormal auricular centers by the ventricular systole; the latter was supposed to induce the formation of a heterotopic stimulus. These premature, abnormal P waves are now explained better by a retrograde conduction of ventricular automatic beats to the auricle. This mechanism can easily be ruled out for the cases described in the present paper.

It is more probable that the same mechanism which causes the auricular rate to change, that is, variation of the vagal tonus in heart block, also influences the site of formation of stimuli or their spread over the auricle, and is in this way responsible for the abnormal form of the P waves in partial heart block.

Lead I the blocked P wave, coming early in diastole, is higher than the conducted P wave. In Lead III the blocked P wave is inverted, whereas the conducted P wave is positive. Prolonged observation of this patient and exercise tests proved that we were dealing with 2:1 block, and not a bigeminal rhythm due to blocked auricular extrasystoles. The P-P interval which includes a ventricular complex measures 0.74 second; the following or the preceding one measures 0.80 second. The abnormal P wave is therefore premature.

Fig. 4 shows two tracings, obtained from two different patients with 2:1 block. The upper tracing was taken from a patient with coronary sclerosis, and the lower from a patient with rheumatic fever. Both tracings are Lead II. In the upper tracing the blocked P wave is

c

b

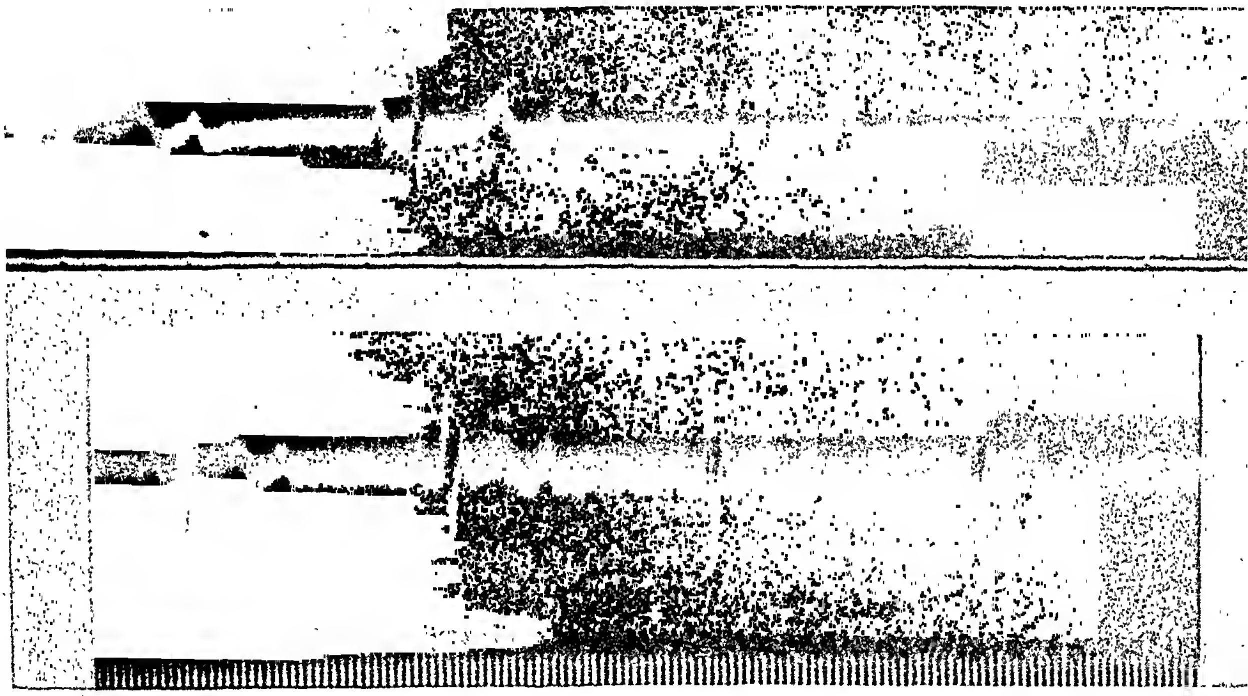

Fig. 4.—Two cases of 2:1 block with alternation in the form of the P waves.

lower, and in the lower tracing it is higher and broader, than the P wave which is conducted to the ventricle. A tracing obtained after an exercise test in the second case, which was published in another connection[8] elsewhere, shows that a conduction disturbance exists, and not extrasystoles. In the upper tracing the P-P intervals which include a ventricular complex measure 0.78, the others 0.84, second. In the bottom tracing the corresponding values are 0.59 and 0.68, respectively. In both cases, therefore, the length of the auricular cycle alternates, and the cycle during which the ventricle contracts is shorter.

DISCUSSION

In all five cases partial heart block existed, and in all cases only those P waves were abnormal which appeared early after a QRS complex.

NEGATIVE DISPLACEMENT OF THE RS-T SEGMENT IN THE ELECTROCARDIOGRAM AND ITS RELATIONSHIPS TO POSITIVE DISPLACEMENT; AN EXPERIMENTAL STUDY

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NEGATIVE displacement of the RS-T segment of the electrocardiogram is common. Study of the literature relating to the mechanisms concerned in its development is, however, not highly illuminating, chiefly, we believe, for two reasons. In the first place, remarkably little experimental work has been done in the attempt to explain it. Second, the relationships of negative displacement in body surface electrocardiograms to potential changes at cardiac surfaces during that interval are not well enough understood.*

Recent studies have indicated that, in general, potential variations of ventricular origin on the surface of the right arm are relatively smaller in magnitude than those of the left arm and left leg,[1-3] and that, in Leads I and II, the patterns of differences of potential usually bear some resemblance to the patterns of potential variation of the left arm and left leg, respectively. Thus, the probability is that, in concordant negative displacement, potential of cardiac origin distributed to both the left arm and left leg is negative during that interval, and that negative potential change is also present over at least part of the epicardial surface of the anterolateral wall of the left ventricle and part of the posterior surface in close contact with the diaphragm. It is therefore possible that the negative displacement recorded in limb leads by Scherf and Boyd[4] after trauma to the inside of the left ventricle reflected negative potential change at posterior and anterolateral surfaces of the left ventricle. Our observations on negative RS-T segment displacement, both experimentally and in acute myocardial infarction, have led us to believe that its direction in Lead II reflects the same direction of potential change on the posterior surface of the left ventricle. Some evidence for that correlation will be furnished in this study.

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Read in abstract, April 20, 1944, at the Inaugural Program of the Instituto Nacional de Cardiologia, Mexico, D. F.

Received for publication May 29, 1944.

*We make the conventional assumption that, when one electrode is placed in contact with a cardiac surface, and the other placed at a distance from the heart, the recurrent patterns of differences of potential corresponding to ventricular activity represent potential fluctuations or variations transmitted to the electrode in contact with the heart, and that, consequently, such electrocardiograms reflect a continuous record of the mean potential variations of the surface area in contact with the electrode.

SUMMARY

Five cases of partial auriculoventricular block are reported, in which those P waves which came early in diastole constantly had an altered shape. In four of these cases, during 2:1 block, the P waves with an abnormal configuration seemed to be slightly premature.

Knowledge of this disturbance will prevent confusion with blocked auricular extrasystoles.

Sometimes this change of form may be due to superimposition of U waves on early P waves. Another possibility is a change in intra-auricular conduction or site of stimulus formation caused by varying vagal tone.

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tion, as had been found to be the case in dogs. This prediction was verified later in 1932[16] by the publieation of ehest leads obtained before and shortly after posterior infarction. In 1938, Wood, Wolferth, and Bellet[17] also showed that negative RS-T segment displacement in a lead with one eleetrode placed over or outside the apex is one of the characteristic ehanges in acute lateral infarction.

In the meantime, Wilson and his co-workers[18] had published their study of bundle branch block, which furnished evidence that patterns of precordial leads tended to resemble those obtained when the exploring eleetrode was placed on eorresponding underlying epicardial surfaees. Another observation by Wilson et al.,[19] whieh is pertinent to our present subject, was that, in the turtle heart, negative RS-T segment displacement eould be recorded at an epicardial area distant from the area of injury. Bellet and Johnston[20] eonfirmed Wood, Wolferth, and Livezey's observation that deprivation of blood supply to the posterior wall produces RS-T segment displacement on the anterior wall opposite in direetion to that obtained over the area deprived of its blood supply.

In eontrast to the meager experimental data bearing on the subjeet of negative RS-T segment displacement, there have been numerous clinical studies in whieh this phenomenon has been reeorded. It is well known that, in addition to its presenee in ehest leads in aeute posterior infaretion, negative displaeement over and above the slight negative displaeement sometimes observed in normal subjeets may be reeorded both in Lead II and in ehest leads following aeute lateral infaretion, during attaeks of angina pectoris, as a digitalis or epinephrine effect, or as a result of other toxie states, and in the so-ealled hyperventilation syndrome.[21] It may be present eonstantly in assoeiation with hypertensive states, and in eertain cases of left ventricular hypertrophy without hypertension. It is found oceasionally during a state of shoek, and may be produeed by earbon monoxide poisoning (Bellet, unpublished observations) or in certain persons by reduetion of the percentage of oxygen in the respired air. It has been shown to be present in certain cases of coronary insufficieney in whieh lesions were suspected, or at least deficiency of oxygen supply, involving the endocardial side of the heart wall.[22] Consequently, because of the clinical importanee of negative displaeement and the unsatisfaetory status of our knowledge as to the modes of its production, an experimental study was undertaken. This study eoneerned itself with efforts to produce negative displaeement in leads made with an exploring electrode on cardiac surfaces, and observations on its relationships to positive displacement.

REPORT OF EXPERIMENTS

Methods.—Dogs were anesthetized deeply by the intraperitoneal administration of 50 mg. (or more, if neeessary) of sodium amytal per kilogram of body weight. A traeheal cannula was tied in plaee, and artificial respiration instituted by means of a motor-driven bellows. The chest was then opened by cutting the ribs bilaterally in the anterior axillary line. The sternum, with attached rib fragments, was thrown back, giving full exposure of the anterior part of the thorax. The peri-

In dealing with RS-T segment displacement in chest leads, one is on somewhat firmer ground than has been the case in limb leads, because correlation between the direction of RS-T potential change on the anterior and left anterolateral aspects of the epicardium and the overlying precordium has been more definitely established. Segment displacement in CR leads, or leads in which the exploring electrode is placed over a part of the precordium and paired with one placed over the spine of the right scapula, we believe, reflects with a high degree of accuracy the direction of potential change at the underlying epicardial surface.

HISTORICAL SUMMARY

Engelmann, in 1873, was the first to demonstrate "monophasic" curves resulting from cardiac injury, according to Burdon-Sanderson and Page[5] (Engelmann's article was not available to us), who confirmed the observation. Bayliss and Starling[6] state that Waller, who showed that "monophasic" curves can also be recorded from mammalian hearts, at first regarded them as a normal phenomenon, but later attributed them to injury. Bayliss and Starling, however, showed beyond question the relationship in the mammalian heart between cardiac injury and what would now be regarded as segment displacement.* These studies long antedate Samojloff's[7] demonstration, in the cold-blooded heart, of RS-T segment displacement after injury, by means of the Einthoven galvanometer. Eppinger and Rothberger[8] obtained evidence to indicate that the direction of RS-T segment displacement in recto-esophageal leads may depend on the part of the heart subjected to injury. The experimental data are open to some question, but the importance of the concept is not.

The awakening of interest in the electrocardiographic study of the effects of coronary obstruction on the myocardium followed Smith's[9] pioneer experimental work on that subject, in which limb leads were used. This was quickly followed by Pardee's[10] observations on electrocardiographic changes in human coronary obstruction. Parkinson and Bedford[11] and Barnes and Whitten[12] then established the limb lead criteria by which infarction involving the anterior and posterior walls of the left ventricle could be differentiated.

In the meantime, chest leads were almost forgotten, although they were used occasionally by Lewis and others to obtain information regarding abnormalities of auricular mechanism. Otto,[13] however, used them in 1929 for the specific purpose of studying experimentally the effects of myocardial injury. He demonstrated that, after injury to the dog's heart, RS-T segment displacement appeared in a lead made with both electrodes on the front of the chest.

In 1932, Wolferth and Wood[14] reported observations on chest leads in human anterior myocardial infarction. With the polarity used at that time, the RS-T segment was recorded as displaced downward. It would now be recognized as positive displacement. On the basis of experimental studies by Wood, Wolferth, and Livezey,[15] completed at the time of that publication but not published until 1933, it was predicted that, in human posterior infarction, the direction of the RS-T segment displacement in chest leads would be opposite to that of anterior infarc-

*In the same paper, Bayliss and Starling concluded that leading from the apex and the right arm yields the largest deflections and is, therefore, favorable.

epicardium with potassium chloride again caused the previously-described segment displacements. This procedure could be repeated several times on the same heart with the same results. In one instance, bathing only the left ventricle with fifth-molar potassium chloride solution caused positive RS-T segment displacement in leads from the surface of that ventricle, and negative RS-T segment displacement from the surface of the right ventricle (Fig. 1, *B-1* and *B-2*). With the development of positive segment displacement, the amplitude of the intrinsic deflection of the QRS complex tended to decrease. As a rule, it extended little, if at all, toward the base line beyond the level of the RS-T segment. The pre-intrinsic deflection was practically uninfluenced by the external application of potassium chloride solutions. The T wave tended to change from the inversion recorded in controls to the upright position.

A single experiment was carried out in which the external surface of the heart was bathed in an extremely dilute solution of ouabain. This produced positive RS-T segment displacement in leads from the epicardial surface which, over the course of several minutes, became quite marked (Fig. 1, *C-1* and *C-2*). The pattern was quite different from that produced by potassium chloride, in that the amplitude of the intrinsic deflection was but little affected, the positive RS-T segment displacement which was maximum at the end of the QRS complex decreased rapidly, and the T wave remained inverted. Negative RS-T segment displacement was recorded when an exploring needle electrode was placed within the left ventricular cavity (Fig. 1, *C-3*). This pattern was different from that produced in the ventricular cavity by the external application of potassium chloride solution, in that the negative displacement which was maximum at the end of the QRS complex diminished rapidly.

II. Injection of fifth-molar potassium chloride solution into the ventricular wall was carried out on two animals. A 20-gauge needle was introduced into the myocardium at an acute angle, and plunged to a point which was thought to be subendocardial. That it was in fact subendocardial was confirmed by post-mortem examination of the heart. Injection of 1 to 2 c.c. of the potassium chloride solution then produced marked negative RS-T segment displacement in leads taken from regions of the epicardium overlying the point of injection (Fig. 1, *D-1* and *D-2*). Continued injection led finally to positive RS-T segment displacement in leads from the same areas (Fig. 1, *D-3*). Injection of the potassium chloride solution into the subepicardial muscle, on the other hand, gave only positive RS-T segment displacement in leads from the overlying epicardium (Fig. 1, *D-4*). These changes were temporary, so that, after waiting a few minutes, the tracings assumed the form of the control tracings. Thereupon, reinjection of potassium chloride solution caused the appearance of the same phenomena. These experiments could be repeated as often as three times on the same heart with comparable results.

III. Scarification of the endocardium was carried out in four dogs. The technique on two animals was as follows: a small metal curette, on the end of a slender steel rod, was introduced through a small slit in the left auricular appendage (which was ligated about the rod to avoid blood loss), and passed down through the mitral valve into the left ventricular cavity. Control tracings were taken. Then injury was produced by turning the curette against the endocardium.

Injury to the endocardium of the left ventricle in one animal by the method described produced positive RS-T segment displacement in

cardium was opened from apex to base and fixed against the lateral chest walls without altering the position of the heart, but allowing free access to all portions of its surface. Only acute experiments were undertaken.

The indifferent electrode in all experiments was a needle electrode inserted into the muscle of the right forepaw. The exploring electrode used to obtain the potential variations of the ventricular cavity was a needle, insulated by baked enamel to within 5 mm. of the tip. Epicardial as well as precordial tracings were obtained with an exploring electrode consisting of a metal shaft, insulated by rubber tubing except at the end, where it was covered with several thicknesses of gauze kept well saturated with warm 0.85 per cent sodium chloride solution. Electrocardiographic results were continually visualized during the experiments by means of a Sanborn cardioscope, and, at appropriate points, tracings were made for permanent records with a Sanborn amplifying type of electrocardiograph.

In almost all experiments, after opening the pericardium and before manipulating the heart, the T waves in direct and semidirect leads, particularly in tracings made over the left ventricle, were found to be inverted, probably because of exposure of the heart to relatively cool air. This phenomenon has been discussed previously by Barnes and Mann.[23] The RS-T segment, however, was usually not significantly displaced, thus allowing satisfactory control tracings for our purposes.

Realizing that slight pressure or friction of an electrode on the underlying cardiac tissue will cause RS-T segment displacement, due caution was observed in the application of the electrodes. This appeared to be especially important when taking tracings from the ventricular cavity. Unless (1) all of the uninsulated tip of the needle electrode was inserted beyond the endocardium and into the ventricular cavity, and (2) contact with the endocardial wall was avoided, RS-T segment elevation was always present. The utmost precautions are therefore required to exclude artifact as a cause of RS-T segment displacement recorded with an electrode in a ventricular cavity. Negative displacement was never recorded in control tracings.

In certain instances, more than one type of experiment was performed on the same heart. However, prior to each experiment, the heart was allowed to return to its original state, at least as far as tracings were concerned, and preliminary control tracings were always made. Each type of experimental observation was carried out on one or more previously unmanipulated hearts.

Types of Experiments and Results.—

I. The epicardial surface of the heart was bathed in warm fifth-molar potassium chloride solution in three animals. Tracings were taken from all parts of the surface of both ventricles and from the endocardial cavity of each ventricle. The changes were always of the same type, and consisted of positive RS-T segment displacement in leads with the exploring electrode anywhere over the outside of either ventricle (as had been anticipated from previous work by others with potassium chloride), in a pad lead from over the surface of the heart, and in Lead II. On the other hand, negative RS-T segment displacement was always recorded when the exploring electrode was inserted into the endocardial cavity of either ventricle (Fig. 1, *A* series). Washing the epicardium with warm 0.85 per cent sodium chloride solution then brought the RS-T segment rapidly back to the isoelectric line, whereupon irrigation of the

leads from within both ventricular cavities (Fig. 2, *A-1* and *A-2*). Leads taken at various points from the anterior, lateral, and posterior surface of both ventricles showed negative RS-T segment displacement in every instance. Post-mortem examination of this heart revealed two distinct areas of injury: one on the anterior endocardial wall of the left ventricle near the apex, measuring 8 by 8 mm., and another on the posterolateral endocardial surface, about 1 cm. square. At both points, only endocardium and the subendocardial muscle had been injured.

Endocardial damage, produced by the same method, to the left ventricle of another dog produced changes of the same type and degree as in the first animal. In addition, however, significant, negative RS-T segment displacement was recorded in Lead II. as well as in three precordial leads, namely, one taken from the right of the sternum, one from over the sternum, and one from the left of the sternum (Fig. 2, *A-3* to *A-12*, inclusive). It was further noted in this experiment that the degree and duration of the negative RS-T segment displacement seemed directly related to the extent of the endocardial injury. After slight injury, the negative RS-T segment displacement on the outside of the heart was of small magnitude and quite transitory, whereas, after more severe damage, the negative displacement was greater and more lasting.

Two earlier experiments of this same type were performed, using a different method of injuring the endocardial surface. The injury produced by this method was slight, and the tracings in these experiments were equivocal. It appears that fairly extensive trauma to the endocardial surface of the heart is necessary, when this method is used, to produce significant negative RS-T segment displacement on the epicardial surface, and therefore on the precordium. The rapid decrease in magnitude of the displacement in these experiments suggested that vascular spasm may have helped to produce it.

IV. Various portions of the epicardial surface of the hearts of four dogs were damaged by cautery, and leads taken from the area of injury, periphery of the injury, and from points on the surface of the heart quite distant from the injury. The technique followed was to heat the tip of an iron rod to redness, and then place it on a previously designated area of the epicardium. The area of damage was usually from 1 to 2 cm. square. Care was taken to sear only the most superficial portion of the subepicardial muscle. Although every effort was made to avoid injury to superficial blood vessels, it was not always possible to be sure that no arterial damage had resulted. Nevertheless, by this method one is able to produce a fairly well-defined area of injury.

The posterior wall of the left ventricle was damaged by this means in three animals. In the first of these experiments the area of injury was small. Leads taken from the damaged area showed positive RS-T segment displacement, whereas leads taken from other areas of the epicardium showed no significant RS-T segment displacement. The second experiment, however, in which the area of damage was larger (approximately 1 cm. square), revealed that, although leads taken from the seared area showed positive RS-T segment displacement, leads taken from normal-appearing epicardium at the periphery of the injured area on the lateral and posterolateral surface of the left ventricle showed negative RS-T segment displacement, and leads from the anterior wall of the left ventricle showed even greater negative RS-T segment displacement. In the third experiment of this sort, no RS-T segment displacement was obtained from the anterior wall of the left ventricle, but positive RS-T segment displacement occurred not only in leads from the

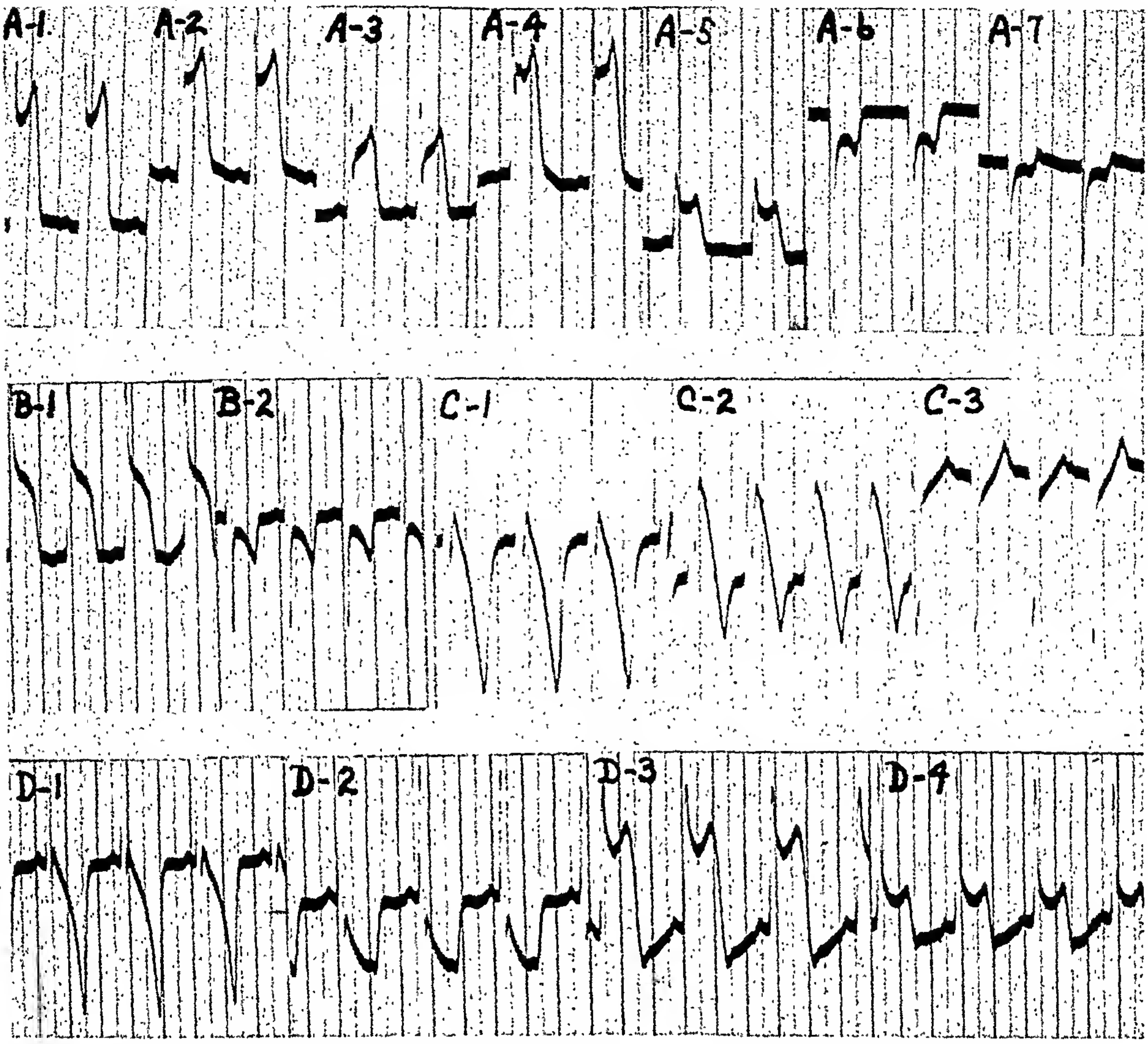

Fig. 1.—In all experiments the exploring electrode was paired with a needle electrode inserted into the right foreleg.

The A series illustrates the results of bathing the entire epicardial surface of the canine heart with fifth-molar solution of potassium chloride. The control tracings with the exploring electrode on the epicardial surface (not shown, but similar to Controls *A-1* to *A-7*, inclusive, Fig. 4) exhibited intrinsic deflections extending from the peak of the preintrinsic deflection to the neighborhood of the base line or below it, negligible RS-T segment displacement, and inverted T waves (as is common when the surface of the heart is exposed). In *A-1* an exploring electrode (covered with gauze and saturated with warm salt solution) was placed at the left ventricular apex, in *A-2* on the lateral wall of the left ventricle, and in *A-3* on the right ventricle near the apex. These illustrate the positive segment displacement obtained over the entire right and left ventricular surface. *A-4* is a pad lead. A large surgical gauze sponge, soaked with warm salt solution, was placed over the surface of the heart, and the exploring electrode was placed on the surface of the sponge overlying the left ventricle. *A-5* is Lead II. (In all leads, the sensitivity of the galvanometer was adjusted to display the pattern, so that amplitude of deflections cannot be compared.) *A-6* is a lead with an exploring needle electrode in the left ventricular cavity, and *A-7* is a similar lead, with the electrode in the right ventricular cavity. Negative displacement had not been present in the control endocardial leads.

In the *B* series the epicardial surface of the left ventricle, only, was bathed with fifth-molar potassium chloride solution. In *B-1*, the exploring electrode was placed on the anterior surface of the left ventricle and, in *B-2*, on the uninvolved surface of the right ventricle.

The *C* series illustrates results obtained by bathing the epicardial surface with a dilute solution of ouabain in salt solution. *C-1* is a control epicardial lead from the anterior wall of the left ventricle. *C-2* was obtained from the same area several minutes after the application of ouabain solution. The change in the RS-T segment and in the depth of T wave was gradual, and *C-2* represents the maximum change. *C-3* was made with a needle electrode in the left ventricular cavity. Note difference of ventricular patterns after application of potassium chloride solution and ouabain.

The *D* series illustrates effects of injection of fifth-molar potassium chloride solution into the ventricular wall. *D-1* is a control obtained from the epicardial surface of the anterior wall of the left ventricle. *D-2* was obtained from the same area after the injection of fifth-molar potassium chloride solution deep into the muscle underlying the electrode. *D-3* shows the effect of further injection into the same area, with probable infiltration of the solution toward the epicardium. *D-4* shows the initial effect of injection of fifth-molar potassium chloride solution in the subepicardial part of the muscle directly under the electrode. The control for this experiment was similar to *D-1*.

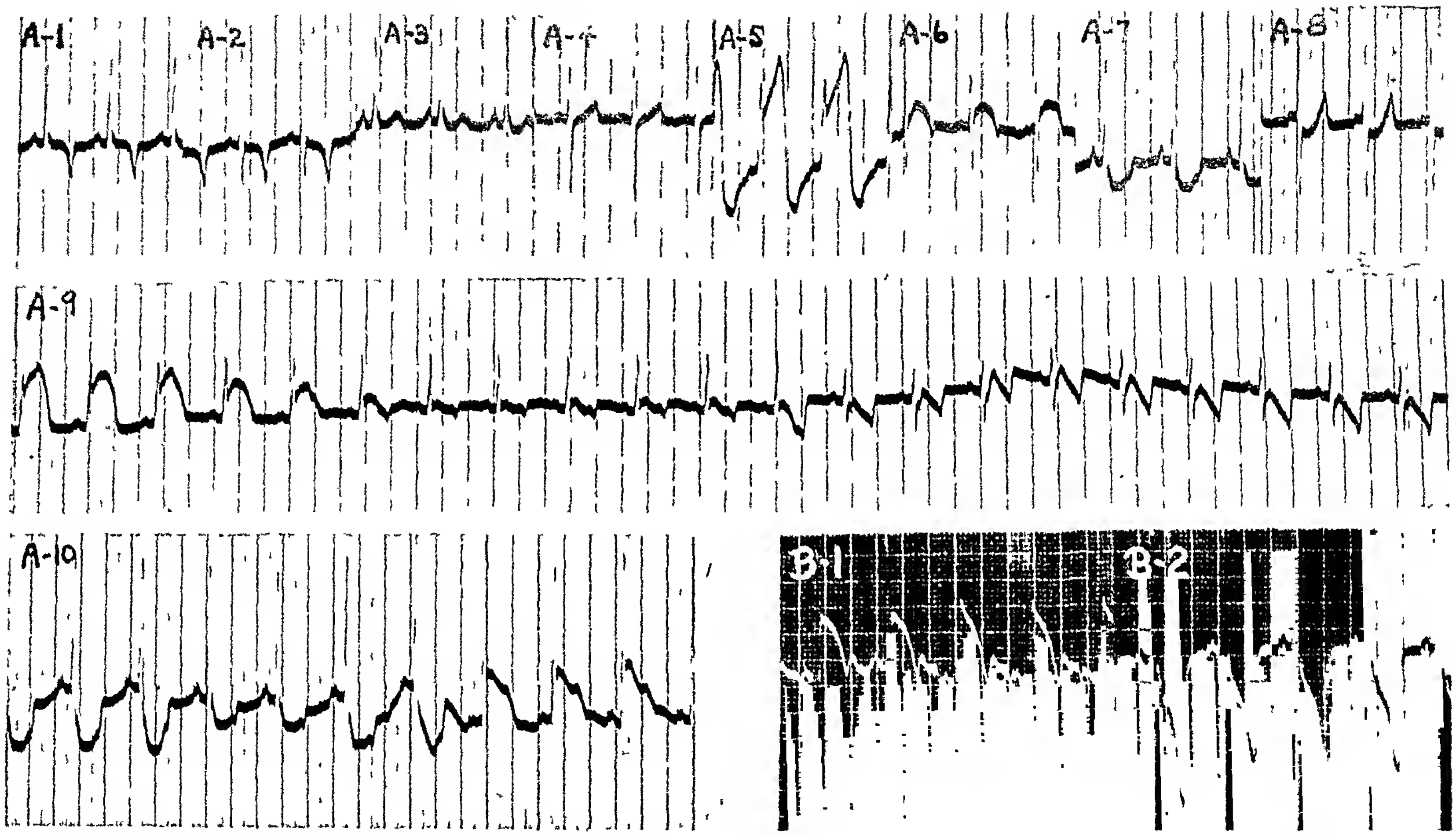

Fig. 3.—Results obtained by cauterization of localized epicardial areas. *A-1* to *A-4*, inclusive, are control epicardial leads. In *A-1* the exploring electrode was placed on the posterior wall of the left ventricle, in *A-2* on the left ventricular apex, in *A-3* on the lateral wall of the left ventricle, and in *A-4* on the lateral wall of the right ventricle. The posterior wall of the left ventricle was then cauterized; the area of the searing was roughly 2 cm. in diameter. In *A-5* the exploring electrode was placed directly over the cauterized surface at about the same position as in *A-1*. In *A-6*, the electrode was placed in the same position as in *A-2*, over presumably uninvolved muscle. This was the only instance in the entire study in which significant positive displacement was recorded over presumably uninvolved muscle. The possibility that the arterial supply to this region was damaged in cauterization could not be ruled out. In *A-7* and *A-8* the positions of the exploring electrode were the same as in *A-3* and *A-4*, respectively. In this experiment the sensitivity of the galvanometer was not changed. Note that in *A-1* and *A-5* the preintrinsic deflection remains about the same, but the intrinsic deflection is greatly reduced in amplitude. The direction of the T wave also changes.

In *A-9* the exploring electrode was slowly moved from the surface of a cauterized area on the anterior wall to a position about 2 cm. beyond the area of injury. In *A-10* the exploring electrode was slowly moved from a point about 1 cm. outside a cauterized area back onto its surface. The more abrupt change in the direction of segment displacement in *A-10* is not due to *more rapid movement of the exploring electrode.*

In *B-1* the exploring electrode was placed over a cauterized area on the posterior wall of the left ventricle, and in *B-2* on the anterior wall of the same ventricle.

injured area, which was low on the posterior wall, but also in leads from the apex (Fig. 3, *A-5* and *A-6*). The latter may have been due to the fact that, in this experiment, a small superficial blood vessel was involved in the injury. However, at the periphery of the lesion on the lateral wall of the left ventricle, negative RS-T segment displacement appeared (Fig. 3, *A-7*). As one gradually moved the electrode from the injured area toward the lateral wall, the positive RS-T segment displacement decreased until the segment became isoelectric, and, finally, negative RS-T segment displacement appeared in leads from unseared tissue bordering on the area of injury (Fig. 3, *A-9*). This sequence of events occurred while moving the electrode not more than 1 centimeter. The zone in which negative RS-T segment displacement alone occurred was, however, considerably wider. The electrode was then placed just outside the burned area, in the zone where negative RS-T segment displacement was

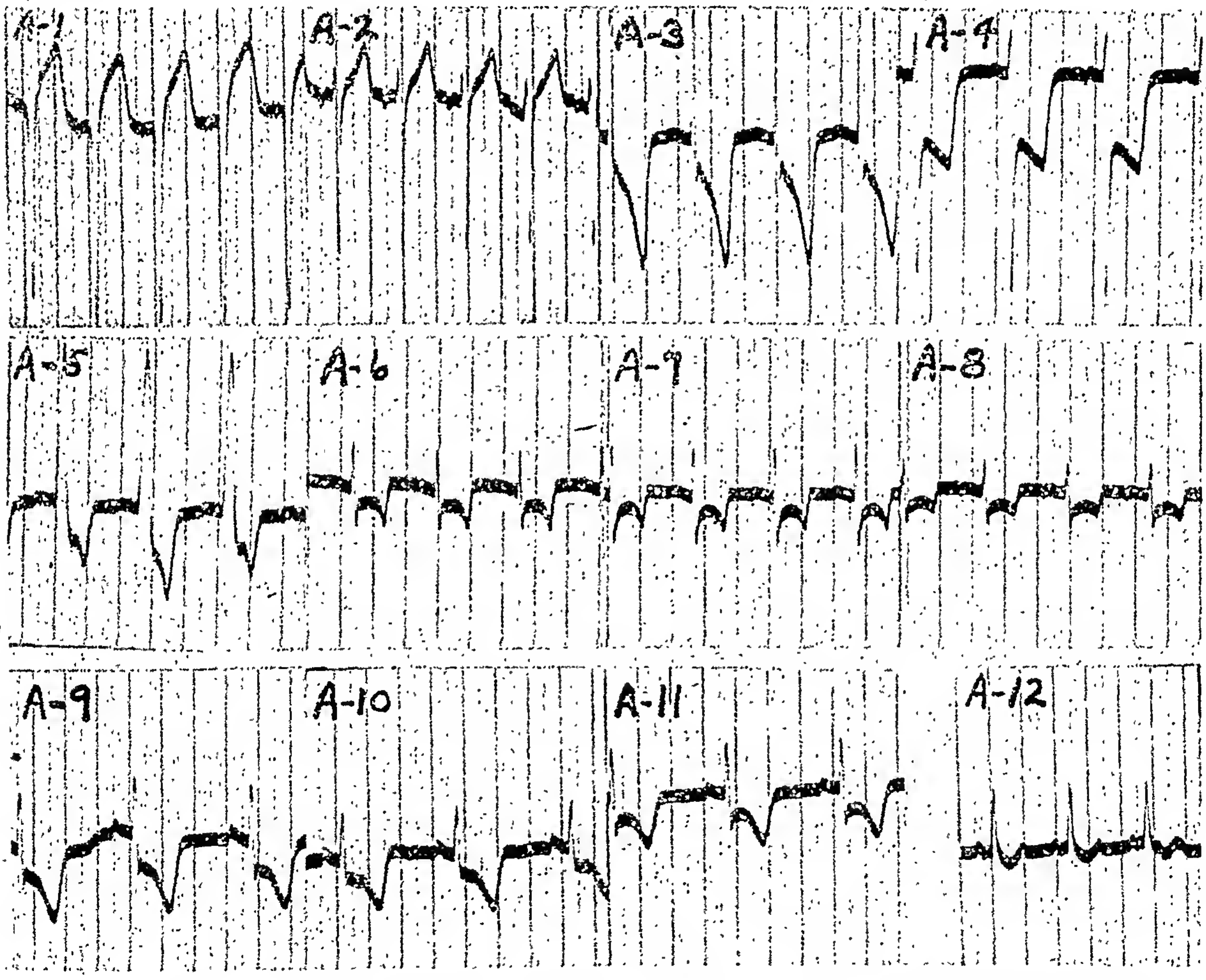

Fig. 2.—Electrocardiograms after extensive trauma to the endocardial side of the canine left ventricle, produced by means of a metal curette inserted through the left auricular appendage and mitral valve. The electrode paired with the exploring electrode was placed on the right foreleg.

A-1 and *A-2* were obtained with a needle electrode in the left and right ventricular cavities, respectively. The positive RS-T segment displacement in these leads is of doubtful significance because of the difficulty of excluding the possibility of contact of the needle with the ventricular wall as a cause of this displacement. In *A-3* the exploring electrode was placed on the epicardial surface of the apex of the left ventricle, in *A-4* on the anterior wall, and in *A-5* on the posterior wall. In *A-6* it was placed on the anterior wall of the right ventricle, in *A-7* over the lateral wall, and in *A-8* over the pulmonary conus. The anterior chest wall was then replaced. *A-9* was made with the exploring electrode on the left side of the anterior chest wall fourth intercostal space, *A-10* over the sternum at the same level, and *A-11* over the right side of the chest wall, fourth intercostal space. *A-12* is Lead II. The controls (not shown) had exhibited no significant segment displacement. The sensitivity of the galvanometer, as in Fig. 1, was adjusted to illustrate patterns, so that differences in amplitude are not comparable. The widened QRS complex in *A-5* suggests that a conduction tract to the posterior wall of the left ventricle was traumatized.

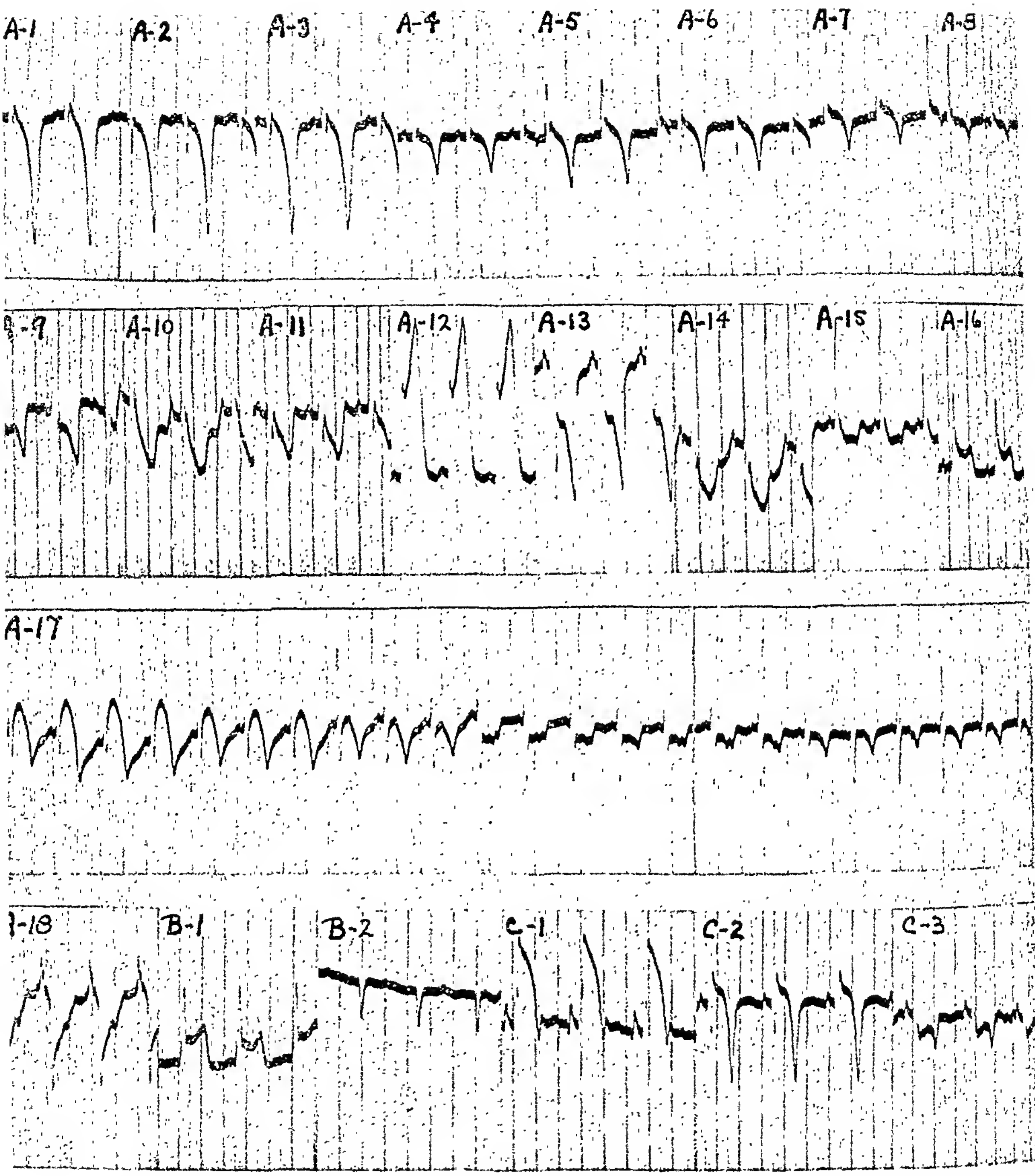

Fig. 4.—*A-1* to *A-8* are control tracings made just prior to complete obstruction of the posterior descending branch of the left circumflex artery. In *A-1* the exploring electrode was placed on the epicardial surface of the anterior wall of the left ventricle, in *A-2* on the apex, in *A-3* on the lateral wall, in *A-4* on the posterior wall, in *A-5* on the anterior wall of the right ventricle, in *A-6* on the lateral wall, and in *A-7* on the posterior wall. *A-8* is Lead II. The artery was then obstructed. *A-9*, *A-10*, *A-11*, and *A-12* were made with the exploring electrode in approximately the same positions as *A-1*, *A-2*, *A-3*, and *A-4*, respectively. In *A-13*, the exploring electrode was on the anterior wall of the right ventricle near the base, and in *A-14* on the posterolateral wall of the right ventricle. *A-15* was a pad lead; a large, moistened, surgical sponge was placed over the anterior surface of the heart, and the exploring electrode was placed on the sponge over the left ventricle. *A-16* is Lead II. In *A-17*, the exploring electrode was moved slowly from what was regarded as the margin of the area of disturbance of arterial blood supply to presumably unin-

(Continued on opposite page.)

recorded. Moving the electrode only a few millimeters toward the burned area caused an abrupt change from negative to positive displacement (Fig. 3, *A-10*).

The anterior epicardial surface of the left ventricle was seared in one animal. Positive RS-T segment displacement was recorded from the injured area, and negative displacement in leads from the posterior wall of the right ventricle (Fig. 3, *B-1* and *B-2*). The changes in ventricular pattern obtained by placing an exploring electrode over a cauterized area are similar to those which follow the application of potassium chloride solution to an epicardial area, not only with respect to segment displacement, but the intrinsic deflection and the T wave, as well.

V. The effect on six animals of complete occlusion of a coronary artery, either by clamp or ligation, was studied. The posterior descending portion of the circumflex branch of the left coronary artery was occluded in four instances, and the anterior descending branch of the left coronary artery in two.

Occlusion of the posterior descending artery resulted in marked positive RS-T segment displacement in leads from that portion of the posterior wall of the left ventricle which was deprived of its blood supply, as well as in Lead II. Leads from the lateral wall of the left ventricle, just peripheral to the area deprived of blood supply, as well as leads from the anterior wall of the left ventricle, showed negative RS-T segment displacement in three of the four experiments (Fig. 4, *A-1* to *A-16*, inclusive). It was possible in one of these experiments to demonstrate an abrupt change from positive to negative displacement by moving the electrode only a few millimeters from the area of ischemia to normal-appearing tissue on the lateral wall of the left ventricle (Fig. 4, *A-17*). In this same experiment, a pad lead taken from the anterior wall of the left ventricle showed negative RS-T segment displacement, as did leads from the surface of both auricles (Fig. 4, *A-18*). Another of this group of experiments gave rise to negative displacement in leads from the anterior and lateral walls of the right ventricle, as well as from the anterior and lateral walls of the left ventricle.

Occlusion of the anterior descending branch of the left coronary artery produced positive RS-T segment displacement in leads from the area of ischemia on the anterior wall of the left ventricle, and, in one instance, from a small portion of the anterior wall of the right ventricle bordering on the interventricular septum. Leads from the posterior wall of the left ventricle showed negative displacement (Fig. 4, *C-1*, *C-2*, and *C-3*), whereas Lead II failed to show significant displacement in either direction. In no instance was it possible to demonstrate significant displacement of the RS-T segment in either direction in leads from within the left ventricular cavity (Fig. 4, *B-1* and *B-2*). The ventricular patterns obtained by placing an exploring electrode on the epicardial surface of a part of the heart muscle which was completely deprived of blood supply were much like those obtained after cauterization or the application of potassium chloride solution. However, at the margin of such a region the amplitude of the intrinsic deflection was relatively little decreased, even though pronounced positive RS-T segment displacement might be present.

VI. Partial occlusion of a coronary artery, produced by various methods, was the object of three types of experiments.

A. In one animal, a small segment of the anterior descending branch of the left coronary artery was dissected free, and control tracings were taken. A slender metal rod was placed alongside the artery, and a liga-

An attempt was made to repeat the above experiment on two other dogs, using the anterior descending branch of the left coronary artery. In neither case were we able to obtain negative displacement over the area partially deprived of blood supply during the time the artery was partially obstructed, although positive displacement was readily obtained. Under these circumstances, however, negative displacement could be recorded from adjacent areas. It could also be recorded from

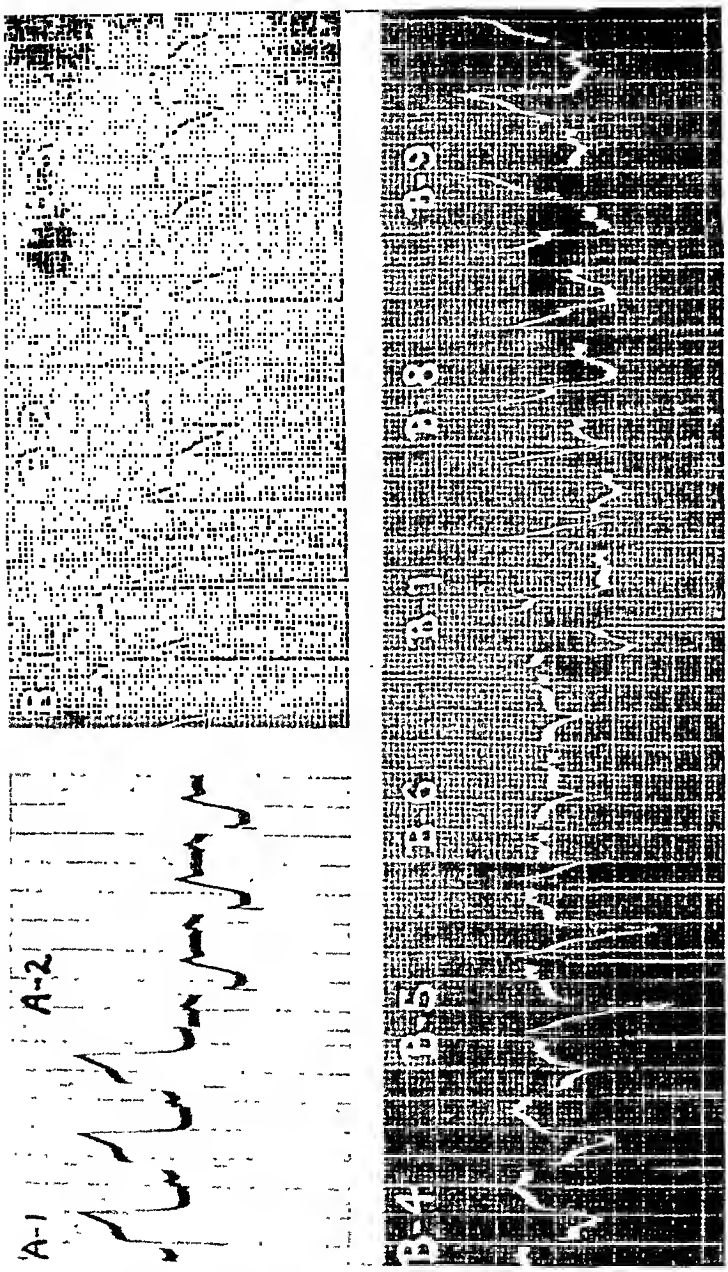

Fig. 5.—Results obtained by partial occlusion of a coronary artery.

In *A-1*, the anterior descending branch of the left coronary artery had been partially occluded by manual traction on a thread passed under the vessel. The exploring electrode was placed on the anterior wall of the left ventricle in the area of distribution of the vessel. In this instance, in spite of very gradual increase in the degree of traction, the initial change in the RS-T segment was positive displacement. Note that the intrinsic deflection was preserved. After release of traction, the direction of segment displacement in the same area became negative, as shown in *A-2*, prior to the return to the pattern obtained before the beginning of the experiment.

The *B* series illustrates the only experiment in which negative displacement was recorded from the epicardial surface without preceding or accompanying significant positive displacement, after partial obstruction of a coronary artery. Similar results were obtained three times in this preparation. *B-1*, a control tracing made with an exploring electrode on the anterior wall near the apex (after dissection of a part of the anterior descending branch of the left coronary artery free from surrounding structures and the insertion of a thread under it), showed slight negative displacement. In *B-2*, made from the same position after slight traction on the thread, the initial change was an increase of the negative displacement, and less deep inversion of the T wave. In *B-3* the exploring electrode was placed posteriorly on the left ventricle near the apex, in *B-4* on the lateral wall, in *B-5* anteriorly at the septum, and in *B-6* over the anterior surface of the right ventricle. The slight positive displacement recorded in *B-6* was no more than is sometimes found in controls. Traction on the artery was then increased. In *B-7*, *B-8*, and *B-9* the position of the exploring electrode was the same as in *B-2*, *B-4*, and *B-5*. Note that in all these positions negative displacement was converted to positive displacement by complete obstruction of the artery.

the area partially or fully deprived of blood supply after release of pressure on the vessel, provided positive displacement had been present during the period of pressure. When positive segment displacement was recorded with an exploring electrode at an epicardial surface after partial deprivation of blood supply to the underlying muscle, the intrinsic deflection, like that recorded from near the margin of a region completely deprived of blood supply, was but little decreased in amplitude.

ture was drawn tight about both rod and artery and tied. The rod was then gently pulled from beneath the ligature, leaving partial compression of the artery. This procedure was repeated, using next a no. 19 needle and finally a no. 24 needle in place of the rod. In all three instances the immediate effect was RS-T segment elevation in leads from the area partially deprived of its blood supply. Immediately after removal of the ligature, negative RS-T segment displacement which was quite transitory, lasting only a minute or two, appeared in leads from the same area where previously RS-T segment elevation had been seen (Fig. 5, *A-1* and *A-2*).

B. A modified Goldblatt clamp was placed about the anterior descending branch of the left coronary artery of another animal, and control tracings were taken. Then gradually increasing pressure was applied to the artery. The primary change was always positive RS-T segment displacement in leads from the ischemic area, with negative RS-T segment displacement in leads from the lateral wall peripheral to this area. After releasing the pressure on the artery, again an immediate, but transitory, negative RS-T segment displacement was seen in leads from the previously ischemic area.

The clamp was applied to the circumflex branch of the left coronary artery in this same animal, and again the primary change was always positive RS-T segment displacement, this time over the posterior and lateral aspects of the left ventricle supplied by this artery, with negative RS-T segment displacement on the anterolateral and anterior walls of the left ventricle and the anterior and lateral walls of the right ventricle. Removal of the arterial compression was followed, as before, by transitory negative displacement in leads from the area where previously positive displacement had been recorded.

C. A fine thread was passed beneath the anterior descending branch of the left coronary artery of a third dog. Progressively increasing traction was applied to the artery by pulling the thread, thus gradually decreasing its lumen. The primary effect was negative RS-T segment displacement in leads from the area whose blood supply was impaired, i.e., the anterior wall of the left ventricle (Fig. 5, *B-1* and *B-2*). Increasing the traction further led to positive displacement in leads from the same area (Fig. 5, *B-7*), and, finally, release of traction altogether gave rise, after a short interval, to transitory negative displacement in leads from the previously ischemic area. During the period that negative displacement was recorded from the surface of the area partially deprived of blood supply, positive displacement was recorded nowhere over the surface of the left ventricle (Fig. 5, *B-3 B-4,* and *B-5*). However, over the anterolateral surface of the right ventricle at some distance from the area of interference with blood supply, slight positive displacement was recorded, although no more than was often noted in controls (Fig. 5, *B-6*).

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volved tissue. Note that the intrinsic deflection is preserved in *A-17*, whereas it is almost lost in *A-12*. Positive RS-T segment displacement changed gradually to negative displacement as the electrode was moved away from the area of involvement. Finally, an area was reached where there was no significant segment displacement. In *A-18* the exploring electrode was placed on the left auricle. The ventricular QRS pattern at that position was of the endocardial type, but the significance of the negative RS-T segment displacement is uncertain.

B-1 was made with the exploring electrode on the anterior wall of the left ventricle after complete obstruction of the anterior descending branch of the left coronary artery. Despite the positive displacement in that lead, no segment displacement was recorded in *B-2*, in which the needle electrode was placed in the left ventricular cavity.

In the *C* series (another preparation), the anterior descending branch was also ligated. *C-1* was obtained with the exploring electrode on the anterior wall of the left ventricle, *C-2* at the apex, and *C-3* on the uninvolved posterior wall of the left ventricle.

less sustained than that which followed the application of potassium chloride deprivation of blood supply, or cauterization.

In a case of hypertensive disease in which there was negative RS-T segment displacement in Lead II and chest leads CR_3 to CR_6, inclusive, an esophageal lead (exploring electrode paired with an electrode over the spine of the right scapula), made with the exploring electrode below the auricular level, also exhibited negative RS-T segment displacement. However, when the exploring electrode was moved to the auricular level

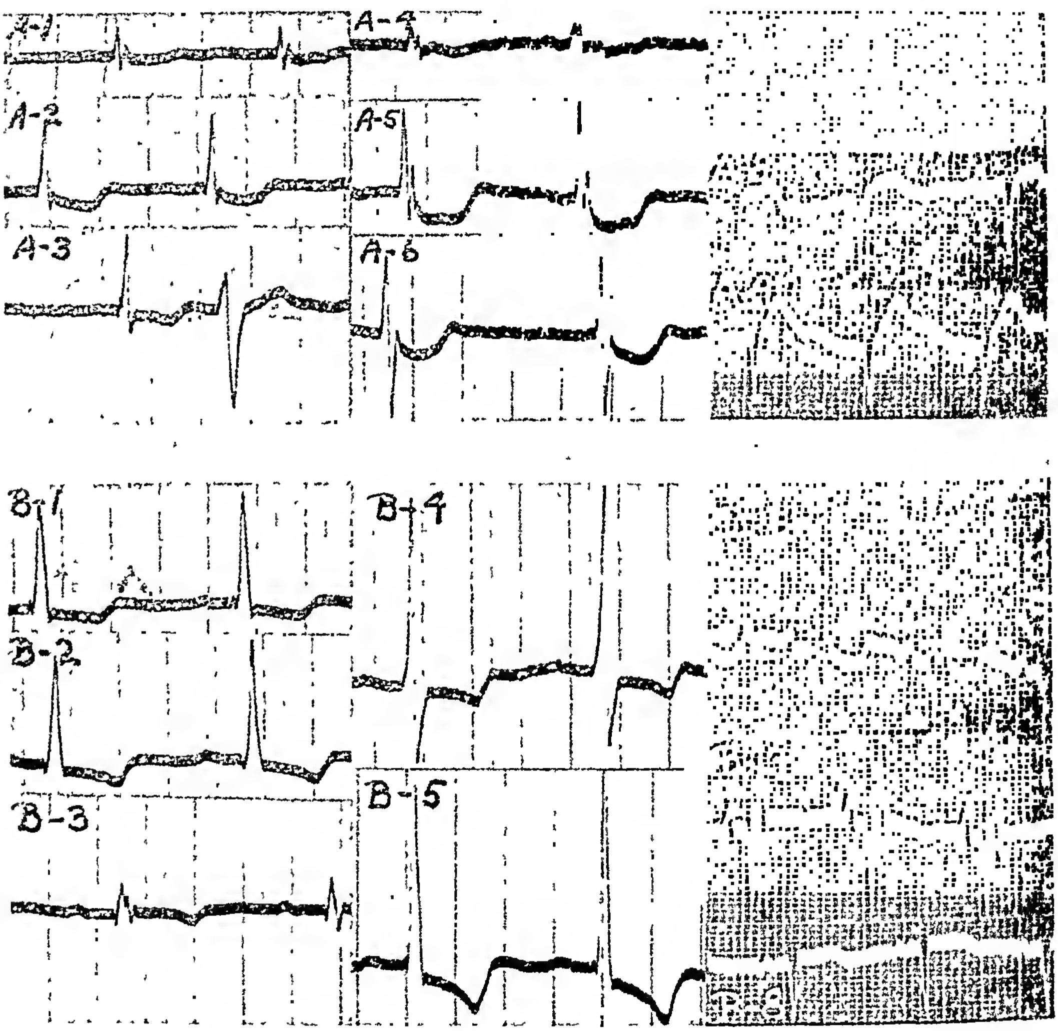

Fig. 7.—The *A* series was obtained from a patient with mitral stenosis, auricular fibrillation, low blood pressure, and no demonstrable left ventricular enlargement. He had been taking digitalis in a dose of 1½ to 3 grains daily to keep the ventricular rate under control. *A-1*, *A-2*, and *A-3* are Leads I, II, and III, respectively, and *A-4*, *A-5*, and *A-6* are leads CR_1, CR_3, and CR_5, respectively. *A-7* was made with the exploring electrode in the esophagus slightly below the auricular level, *A-8* at the auricular level, and *A-9* slightly above the auricular level. The QRS pattern is of the endocardial type in *A-8* and *A-9*, positive RS-T segment displacement is present in *A-8*, in contrast to body surface leads, and the T wave is abnormally upright in *A-8* and *A-9*.

The *B* series was obtained from a patient with hypertension and left ventricular hypertrophy. Digitalis had not been administered. *B-1*, *B-2*, and *B-3* are Leads I, II, and III, respectively. *B-4* and *B-5* are leads CR_3 and CR_5 respectively. In *B-6*, the exploring electrode was in the esophagus below the auricular level, in *B-7*, at the auricular level, and in *B-8* slightly above the auricular level. Note the change in RS-T segment displacement from slightly negative to slightly positive as the exploring electrode is moved from below the auricular level to that region and above. In this case the pure endocardial type of QRS complex was not obtained until the exploring electrode was slightly above the auricular level.

VII. Miscellaneous observations. During the course of the experiments described above, it was noted that negative potential change during the RS-T interval, produced over the surface of uninvolved muscle by involvement elsewhere, could be converted to positive change by the direct application of potassium chloride solution or by deprivation of the arterial blood supply to the underlying muscle (Fig. 6, *D* series).

The application of fifth-molar lithium lactate solution or fifth-molar lithium citrate solution to an epicardial surface produced, at most, slight positive RS-T potential change. One hundredth-molar potassium chloride solution, however, produced immediate positive displacement comparable to that caused by the fifth-molar potassium chloride solution used in the experiments described above (Fig. 6, *A-1* and *A-2*). The application of fifth-molar calcium chloride solution to an epicardial surface produced positive change, but it was much less in magnitude than

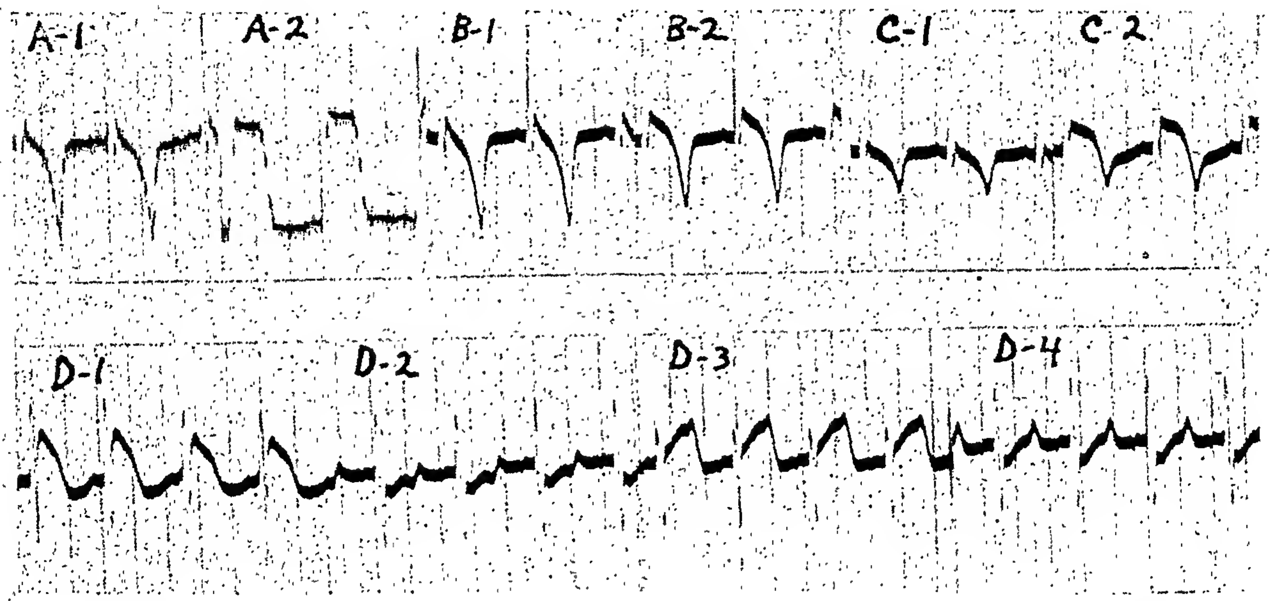

Fig. 6.—*A-1* is a control tracing made with an exploring electrode on the anterior surface of the left ventricle. *A-2* was obtained from the same area less than one minute after the application of one hundredth-molar potassium chloride solution.

B-1 is a control from the same area after repeated washing with warm salt solution. *B-2* shows the maximum change observed after the application of fifth-molar calcium chloride solution to this area.

C-1 is a control tracing from the lateral wall of the left ventricle. *C-2* shows the maximum change obtained from the same region after the application of fifth-molar calcium chloride solution.

In *D-1* the exploring electrode was placed on the posterior wall of the left ventricle after application of a dilute solution of epinephrine to that region. In *D-2*, which was made immediately after *D-1*, the exploring electrode was placed on the anterolateral wall of the left ventricle, which had not been exposed to epinephrine. *D-3* was made from the same general area as *D-2*, after temporary obstruction of blood supply to that region. *D-4* was made after release of obstruction. Note the differences in pattern produced by potassium chloride, calcium chloride, and epinephrine solutions, and the fact that secondary negative segment displacement obtained over uninvolved areas can be converted to positive displacement by obstruction of blood supply to that region.

that produced by one hundredth-molar potassium chloride solution (Fig. 6, *B* and *C* series). The displacement in leads from such areas was sustained longer than that produced by ouabain, but not as long as that produced by potassium chloride. The intrinsic deflection was but little affected. The magnitude of the inverted T wave of the control tracing was lessened, but its direction was not changed. Extremely dilute solutions of epinephrine produced positive displacement in leads over the area of application, and negative displacement elsewhere. The displacement, like that produced by applying calcium chloride solutions, was

excitation of the muscle fibers directly under that surface. All other changes in potential transmitted to the electrode during the QRS complex represent electrical activity elsewhere, and are therefore classed as extrinsic. Obviously, in all parts of the ventricles except the part activated first, the intrinsic deflection cannot be recorded apart from potential variation caused by extrinsic electrical activity. Nevertheless, the intrinsic deflection is easily recognized, although it is subject to distortion, depending upon the extrinsic effects which occur at the same time. This distortion of the intrinsic deflection, however, does not impair the usefulness of the concepts developed by Lewis regarding the QRS complex. It seems to us, on the basis of the observations reported above, that the concept of differentiation between intrinsic and extrinsic effects can be extended with advantage to the RS-T segment. The possibility exists that it may also be useful in the case of the T wave. However, in order to avoid confusion in nomenclature, we shall use the terms primary and secondary instead of intrinsic and extrinsic. By RS-T segment displacement of primary type we mean displacement resulting from abnormal physicochemical disturbance in the muscle fibers directly under the electrode. By displacement of secondary type, we mean the displacement that can be recorded over the surface of uninvolved muscle; the potential change is induced at that surface by involvement elsewhere.

The RS-T segment possesses advantages over the QRS complex and the T wave for the study of potential change of what we call primary and secondary type. In the first place, if suitable precautions are taken, RS-T segment displacement recorded over the surface of healthy heart muscle is so small in magnitude, compared with that which can be produced by experimental procedures, that it can be disregarded. Second, the region in which RS-T segment displacement is produced experimentally can be localized so accurately in certain types of experiments that, except at the margin of the area of involvement, one can be confident that he is dealing either with primary or secondary effects, and not with a mixture of both.

In the experimental results reported above, the primary RS-T segment potential change, with one possible exception, which will be discussed below, was always positive, and the secondary change, wherever it occurred, was always negative. Thus, positive potential change produced at the epicardial surface by local disturbance caused negative displacement in leads from the endocardial cavities; acute trauma to the endocardial side of the heart wall produced negative displacement from the uninvolved epicardial surfaces; positive potential change produced by the application of certain chemical solutions or cautery to a part of the epicardial surface produced negative potential change at other uninvolved epicardial surfaces. Complete obstruction of blood supply to one part of the heart wall, producing positive RS-T segment

or to a position slightly above it, positive RS-T segment displacement was recorded (Fig. 7, *B* series).

The electrocardiogram of a well-digitalized patient with mitral stenosis and auricular fibrillation, but without hypertension or demonstrable left ventricular hypertrophy, showed negative RS-T segment displacement in Lead II and the chest leads, but exhibited positive displacement in a lead made with the exploring electrode at the auricular level of the esophagus (Fig. 7, *A* series).

DISCUSSION

One of the important unsolved problems of electrocardiography concerns itself with the physicochemical mechanism or mechanisms responsible for RS-T segment displacement. The solution of this problem would probably constitute a significant advance toward a clearer understanding of the bioelectric phenomena responsible for electrocardiographic deflections in general. The work of Osterhout[24] with nitella cells and his model of the potassium effect emphasize the importance of change in the permeability of the cell membrane, the migration of K^+ ions to the outer surface of the cell membrane during excitation, and the presence of the "R" substance as essential factors in the development of potential changes. Possibly similar phenomena are concerned in the excitation of heart muscle fibers, although the part that they may play in the development of the changes in potential which are responsible for the electrocardiogram is not as yet known.

During the course of this study, although our interest was focused on the distribution of pathologic positive and negative RS-T segment displacement, the qualitative differences in ventricular patterns produced by some of the experimental procedures described above were so striking that they could scarcely escape notice.

In the analysis of these patterns the behavior of the intrinsic deflection and T wave, as well as the RS-T segment, requires consideration. However, one need only observe the differences in the characteristics of the segment displacement produced by the application of potassium, calcium and ouabain solutions to realize that the theoretical explanations offered in the past as to its nature are not adequate. One point, at least, seems clear: the RS-T segment cannot under all circumstances be merely the reflection of continuous current flow during diastole, as would be the case if it were due solely to incomplete repolarization. Its characteristics must be determined, at least to some extent, by what takes place or fails to take place during systole.

Electrocardiography owes a great debt to Lewis and his collaborators[25] for the differentiation between the intrinsic deflection of the QRS complex and the deflections of extrinsic origin. The intrinsic deflection, according to Lewis' views, reflects the sharp fall in potential at the part of the surface of the heart in contact with an electrode at the onset of

primary positive potential from the surface over the lesion. The direction of segment displacement may therefore be upward or downward, depending upon which effect dominates.

If the exploring electrode is paired with one placed on a surface position which has relatively slight potential variation, such as over the spine of the right scapula (or even the right arm), positive RS-T segment displacement of magnitude sufficient to be abnormal in any precordial lead means that a part of the myocardium just beneath the epicardial surface, presenting toward the electrode, is involved. Negative displacement, on the other hand, signifies one of the following: (1) If the involvement extends to the ventricular epicardial surface, that part of the surface does not lie directly under the electrode, but might be situated anywhere outside the zone near the electrode, where involvement could dominate the direction of displacement. (2) Involvement limited to the endocardial aspects of the wall produces negative displacement, even when the site of injury underlies the electrode directly. (3) Partial deprivation of blood supply in the region directly underlying the electrode can produce negative displacement, although, as stated above, this may be a secondary effect caused by the production of positive displacement on the endocardial side.

In Lead II, or a lead in which the electrode on the leg is paired with one placed over the spine of the right scapula in order to minimize interference with the potential variations of the left leg, abnormal positive RS-T segment displacement indicates that the lesion involves a subepicardial region in close relationship with the diaphragm. Negative displacement, on the other hand, signifies (1) that the lesion involves some other part of the surface, (2) that the lesion is limited to the endocardial aspect of the wall not reaching the subepicardial region, or (3) that there is merely a partial deprivation of blood supply in some part of the heart.

The direction of potential variation during the RS-T interval in the esophagus well below the auricular level is the same as that of the left leg, and therefore adds no information of value regarding the segment. At the auricular level, however, the potential of the exploring electrode probably reflects the potential variations of the left ventricular cavity,[26] so that positive segment displacement signifies involvement of the endocardial aspects of the left ventricular wall. Our inability to obtain displacement in leads from the left ventricular cavity after occlusion of coronary arteries was unexpected. We finally concluded that positive potential change might have been counterbalanced by secondary negative change at uninvolved areas, so that the two tended to neutralize each other.

The experiments reported above explain why RS-T segment displacement in acute lateral infarction has the characteristics described by Wood, Wolferth, and Bellet,[17] in 1938. Negative RS-T segment deflection is recorded in precordial leads and in Lead II in lateral infarction

displacement in leads with the exploring electrode over the surface of such an area, caused widespread negative displacement in leads from uninvolved areas.

As far as we are aware, it has not been demonstrated that negative RS-T segment potential changes can be produced at a cardiac surface by direct involvement of the fibers just under that surface. Whether the negative displacement observed once in this study after partial obstruction of a vessel, or the negative displacement recorded during the recovery period following positive displacement, is a primary effect, and reflects involvement of the fibers under the electrode, or is a secondary or induced effect resulting from positive potential change in the deeper layers of the heart wall, was not ascertained in these experiments. The latter explanation, however, seems more likely.

The results of these experiments, we believe, have a bearing on the interpretation of the patterns of RS-T segment displacement in human electrocardiograms. It appears safe to say that abnormal positive displacement in a chest lead reflects involvement of fibers at the epicardial surface, or near the surface underlying the exploring chest electrode. It is well known that there is a tremendous decrement in potential variation between an epicardial surface and the overlying precordial surface, which introduces a quantitative difference between leads made with the exploring electrode on each of these surfaces. This, however, is not so important in interpretation as the qualitative difference in patterns caused by essential differences in the relationships of electrode to parts of the epicardial surface. In an epicardial lead, the pattern of potential variation of the exploring electrode almost certainly depends on the mean potential variation at each instant of that part of the surface in direct contact with the electrode. In the case of the RS-T segment, such variation may be primary or secondary, or a combination of both. If the change from one type to the other in adjacent areas is abrupt, such distribution should be demonstrable by exploration with an electrode which has a small area of contact with the epicardium. That this is the case is strikingly illustrated by the experiments in which the electrode was slowly moved across the margin of an area of involvement and the abrupt change from positive to negative displacement observed. Such sudden changes cannot be obtained by exploring positions equally near each other on the chest wall. The reason for this is that an electrode with a comparable area of contact on the chest wall must necessarily tap the potential variations of a much larger epicardial area; the influence of each unit area on the electrode doubtless depends on the properties of the electrical pathway between that area and the electrode. Thus, if an acute lesion involves the anterior surface of the left ventricle, an exploring electrode placed on the chest wall over the right ventricle will, in all probability, have transmitted to it secondary negative potential derived from currents at the surface of that ventricle, and

privation of blood supply is primary or secondary in origin. We have long been puzzled by the fact that, during an attack of angina pectoris, the electrocardiogram usually shows negative RS-T segment displacement, and thus resembles the pattern of acute lateral infarction. It did not seem reasonable to suppose that angina pectoris is usually accompanied by deprivation of blood supply to the lateral wall of the left ventricle alone. However, if the true explanation for the negative displacement observed during attacks of angina pectoris is anoxemia of the endocardial aspect of the wall, the electrocardiogram would exhibit negative displacement, irrespective of the artery or part of the heart affected. The negative displacement recorded in certain cases of shock, carbon monoxide poisoning, advanced coronary insufficiency without actual infarction, and even the hyperventilation syndrome could be easily accounted for by assuming selective involvement of the endocardial side of the heart wall. The evidence for this view, however, is not complete. Further study of partial deprivation of blood supply may throw more light on the problem. The facility of occurrence of negative RS-T segment displacement clinically, under circumstances of presumed oxygen want, and the difficulty we have experienced in trying to produce it experimentally, with the exploring electrode directly over the area of involvement, by partial obstruction of an artery, are not as yet completely reconciled.

It now seems likely that the negative RS-T segment displacement sometimes recorded in precordial leads early in the course of an attack of acute coronary occlusion, which later develop the typical pattern of infarction of the anterior wall, with positive segment displacement in the same leads, reflects a state of partial deprivation of blood supply prior to complete occlusion. The same explanation may apply in the case of the reversal of the direction of segment displacement in Lead II in posterior infarction.

The reason why the intrinsic deflection is sometimes relatively unaffected when positive segment potential change is produced at a cardiac surface, and is sometimes markedly diminished, so that what has been inelegantly called a "high take-off" is produced, was not clearly ascertained in the course of these experiments. In the experiments on obstruction of arterial blood supply, its magnitude seemed to be decreased most when the obstruction was complete. It is therefore probable that, when the deflection in a chest lead which corresponds to the intrinsic deflection in an epicardial lead is markedly decreased in amplitude in comparison with its preintrinsic-like partner, the inference may be drawn that the obstruction is high grade or complete. This statement obviously applies only to the early stages of acute occlusion, before changes in the first part of the QRS complex make their appearance. The sign is of little value in Leads I and III because of interference effects, but, from observations on cases of acute posterior infarction in the early stages, we believe that a marked decrease in the amplitude of

because the lesion is located in such a position that secondary negative displacement over the anterior surface of the heart and over the part of the heart in contact with the diaphragm governs the direction of segment displacement in those leads. If it were possible to place an electrode directly over the area of involvement, as can be done in experimental animals, primary positive displacement would doubtless be recorded if the lesion extended close to the epicardial surface. If, however, anoxemia also involves the anterior or diaphragmatic surface of the heart, this part of the lesion will dominate the direction of RS-T segment displacement in anterior chest leads and Lead II, respectively.

In the paper on lateral infarction, the close resemblance between the patterns of displacement produced by that lesion and a digitalis effect was pointed out. The recent illuminating studies by Barnes and his colleagues[27] indicate that digitalis effects are exerted preponderantly on the endocardial side of the cardiac wall, and that changes produced by prolonged anoxemia are also located on the endocardial side. Our experiments, as has been pointed out, have indicated that endocardial lesions produce the secondary type (negative) of potential change at epicardial areas. Consequently, it is probably not possible to distinguish, in body surface leads, the patterns of RS-T segment displacement which result from a lesion on the lateral wall of the left ventricle, even though it involves the epicardial surface, from one which involves the endocardial side of the ventricular wall, unless large conduction tracts become involved in the endocardial lesion. To what extent the direction of segment displacement obtained with an exploring electrode in the esophagus at the auricular level may help to clarify this situation will have to await further data. In the case of digitalis effect, the positive displacement recorded from the appropriate levels in the esophagus is in harmony with Barnes' observation that the digitalis effect is primarily on the endocardial side. Thus, the negative displacement recorded in the body surface leads is presumably of the secondary, or induced, type. The results of bathing the epicardial surface with a solution of ouabain, after which the direction of RS-T segment displacement is the opposite of that which occurs after administration of digitalis by mouth or parenterally, are also in accord with this concept. In view of the fact that the relationships of positive and negative segment displacement are the same in cases of hypertension as with digitalis effect, it seems probable that the source of the disturbance responsible for segment displacement is on the endocardial side, and that the negative displacement recorded in body surface leads likewise reflects negative displacement of secondary type at epicardial surfaces.

In order to reach a more complete understanding of RS-T segment displacement, a far more extended study, of partial deprivation of blood supply than the exigencies of the times have permitted us to make is necessary. However, from the practical viewpoint, it makes little difference whether the negative displacement recorded after partial de-

receives a contribution from the abnormal electrical activity on the endocardial side. The complexity of the subject, however, is such that as yet little can be said about it.

SUMMARY AND CONCLUSIONS

1. RS-T segment displacement recorded with one electrode on a ventricular surface or in a ventricular cavity may be classified as primary or secondary; this is analogous to Lewis' classification of the deflections of the QRS complex as intrinsic and extrinsic. Primary displacement is defined as that which results from abnormal current flow originating in the muscle in close relationship with the exploring electrode, and secondary displacement as that which results from abnormal current flow originating in any other part or parts of the ventricles.

2. The patterns of both primary and secondary displacement vary in certain respects, depending upon the agent used to produce the displacement. This is not in accord with the view that current flow during diastole is solely responsible for RS-T segment displacement recorded during systole, but suggests that, under certain circumstances at least, systolic events play a part.

3. The production of a positive RS-T segment potential change (primary type) at one part of the heart by such diverse means as dilute solutions of potassium chloride, ouabain, or epinephrine, cauterization, trauma, or complete deprivation of blood supply is accompanied by the occurrence of a negative potential change (secondary type) over uninvolved ventricular surfaces.

a. The production of a positive RS-T segment potential change over the entire epicardial surface by solutions of potassium chloride or ouabain causes a corresponding negative potential change within the ventricular cavities.

b. The production of positive RS-T segment potential change over the epicardial surface of the left ventricle causes negative change over the epicardial surface of the right ventricle.

c. The injection of potassium chloride solution toward the endocardial side of the left ventricular wall produces a negative RS-T segment potential change at the overlying epicardial surface, but injection just beneath that surface produces a positive change.

d. Extensive trauma to the endocardial side of the myocardium produces a negative RS-T segment potential change at ventricular epicardial surfaces.

e. Extensive cauterization of ventricular epicardial surfaces produces a positive RS-T segment potential change over the area cauterized and a negative change in other areas. In the one exception recorded, it is possible that an artery supplying a region beyond the area of cauterization had been destroyed. The reversal in direction of potential change at the margin of the area of injury may be abrupt.

the intrinsic-like deflection in Lead II, with "high take-off," points to high-grade deprivation of arterial blood supply to the area involved.

Although this study did not concern itself with the T wave, we wish to comment on the possible importance of intrinsic and extrinsic, or what, in the case of the RS-T segment, we have called primary and secondary, electrical effects on the form of that deflection. This problem is difficult to study because of the fact that the electrical activity responsible for the T wave is present over all parts of both ventricles at approximately the same time. The importance of subepicardial abnormality in producing changes in the T-wave potential variation at the overlying surface, and consequently in significant body surface leads, is probably just as great as in the case of RS-T segment displacement. So much is easily demonstrable by experiments such as those reported above. Moreover, it has long been known that T-wave changes may be conspicuous in the course of acute pericarditis, in which, presumably, only the subepicardial muscle is involved. It would, however, be of interest to know how secondary effects influence the form of the T wave. Some information on this point can be obtained from a study of left bundle branch block, in which there is so much asynchronism of T-wave deflection of right and left ventricular origin that the summits of the two can be separated. Wolferth and Livezey plan to publish some of the observations on bundle branch block in a subsequent paper, but the following may be said at present: In left bundle branch block, the relatively early, right-ventricular T wave, as recorded in precordial leads with an electrode placed over the right ventricle, has always been upright, in our experience, and tends to be of decidedly greater amplitude than it is when no bundle branch block is present. Over the left ventricle, however, this part of the T wave is always slightly inverted, but the terminal portion of the T wave, which is presumably due to aberrant left ventricular activity, is always upright and of small amplitude. It would appear, therefore, that the large T wave recorded with an exploring electrode over the right ventricle in left bundle branch block is caused by the absence of any effect of secondary potential variation derived from left ventricular activity on the epicardium of the right ventricle, which, under normal circumstances, tends to neutralize, at least to some extent, the primary effect produced locally. The slight inversion of the T wave recorded over the left ventricle, corresponding in time with the large upright T wave over the right ventricle, suggests that secondary right ventricular effects at the surface of the left ventricle are almost negligible. A fragment of evidence with possible bearing on this problem was obtained in the present study. In the normal, the T wave with an exploring electrode in the esophagus at the level of the auricle, or slightly above, is always negative.[28] However, in Fig. 7, it is noted that the T waves obtained with the exploring electrode at those levels were distinctly positive. It is therefore possible that the deformity of the T wave at the epicardial surface caused by digitalis

of relatively slight potential variation, such as the spine of the right scapula or even the right arm, reflects the direction of potential change in the left endocardial cavity during that interval. In certain cases such a lead may furnish evidence of value as to the location, and possibly also the nature, of myocardial involvement.

8. It is probable that the concept of primary and secondary effects applies to the formation of the T-wave potential change at any cardiac surface area in somewhat the same manner as in the case of RS-T segment potential change, although, under these circumstances, primary and secondary effects coexist. For this reason the demonstration of such relationships, particularly from the quantitative viewpoint, is far more difficult than in the case of the RS-T segment.

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f. Complete obstruction of a coronary artery produces a positive RS-T segment potential change at the epicardial surface deprived of its blood supply, and a negative change in other epicardial areas. The reversal in direction occurs at the margin of the area of involvement.

g. Partial obstruction of a coronary artery usually produces either no significant potential change during the RS-T interval at the epicardial surface of the area supplied by that artery, or a positive change, depending upon the grade of obstruction. Moreover, the amplitude of the intrinsic deflection of the QRS complex is affected less by partial, than by complete, obstruction. After cessation of partial obstruction, or even transient complete obstruction, the positive change is converted to negative, and this persists for a short period prior to disappearance of pathologic potential change. For the observation and recording of such events, continuous use of the cardioscope is almost indispensable.

h. In one set of experiments only, of many attempts, using three different methods of producing partial obstruction, was it possible to obtain a negative RS-T segment potential change at the epicardial surface partially deprived of blood supply, without preceding positive change. In this experiment a negative change was also recorded from adjacent areas. An increase in the grade of obstruction produced a positive change over the involved surface.

4. The negative RS-T segment displacement recorded with an exploring electrode over an epicardial region after cessation of obstruction may be of secondary type because of selective involvement of the endocardial side of the myocardial wall.

5. There is as yet no definite evidence that a negative RS-T segment potential change can be produced at a cardiac surface other than as a secondary affect caused by pathologic currents originating elsewhere in the myocardium.

6. A positive or negative RS-T segment displacement recorded by placing an exploring electrode over an anterior or anterolateral epicardial area tends to be associated with a corresponding positive or negative RS-T segment displacement in a chest lead in which the exploring electrode is placed on the surface directly over that epicardial area. It is also highly probable that a positive or negative potential change at a part of the epicardial surface in contact with the diaphragm (during the RS-T interval) is associated with a corresponding positive or negative displacement in Lead II. Judging from the relationships observed in the experiments described above, the patterns of RS-T segment displacement recorded in body surface leads can be accounted for in a much more satisfactory manner than was possible in the past.

7. Although the matter requires much further study, there is already strong evidence to indicate that the direction of RS-T segment displacement recorded with an exploring electrode in the esophagus at the auricular level, or slightly above it, paired with an electrode on an area

THE TREATMENT OF ORTHOSTATIC HYPOTENSION

With Particular Reference to the Use of Desoxycorticosterone

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BRADBURY and Eggleston[1] described a syndrome which they designated "postural hypotension." This syndrome consists of marked weakness, dizziness, normal blood pressure in the sitting or reclining positions, marked fall in blood pressure in the upright position, an insignificant elevation in the cardiac rate in the upright position, impairment of sweating, and accentuation of symptoms in hot weather. They thought that these symptoms indicated a defect in the function of the sympathetic nervous system. This concept has continued to dominate discussions concerning the etiology, as shown by the report of Ellis and Haynes,[2] who emphasized the relationship between orthostatic hypotension* and disease of the nervous system. Jeffers, Montgomery, and Burton,[3] Stead and Ebert,[4] Freeman and Robertson,[5] and Laufer[6] have confirmed these observations and interpretations, and have furthered the concept that the syndrome is due to inadequate vasomotor function. It has been demonstrated repeatedly, however, that this abnormality may occur in cases in which no disease of the nervous system can be discovered by clinical means.

Although defects in the reflex sympathetic vasomotor control and increase in the cardiac rate in the upright position have been thought generally to be the most important factors in the pathogenesis of this abnormality, MacLean and Allen[7] and MacLean, Allen, and Magath[8] have suggested and presented evidence that the fault lies in failure to maintain adequate return of venous blood to the heart. Hallock and Evans[9] have shown that there are a decrease in blood volume and hemoconcentration in this disease when the patient is in the upright posture, and they have suggested that abnormal filtration rates aggravate the circulatory embarrassment. Hallock and Evans have also observed, as have others, including myself, that this condition may be associated with orthostatic tachycardia.

The treatment of orthostatic hypotension has consisted of various mechanical procedures, such as tight abdominal and leg binders, the "head-up" sleeping position described by MacLean and Allen,[7] the

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Received for publication June 2, 1944.

*The desoxycorticosterone used in this study was "Cortate," Schering Corporation brand of synthetic desoxycorticosterone in sesame oil. Generous amounts of the substance were supplied by Dr. W. R. Bond, Medical Research Division, Schering Corporation, Bloomfield, N. J.

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readings were made during that period. Benzedrine and ephedrine were used for a few days, but it was necessary to discontinue them because of the resulting nervousness and insomnia.

Paredrine hydrobromide by mouth was then tried, with considerable benefit for a while. In time, however, she appeared to develop tolerance, which required increasing the dose and shortening the interval between doses. Finally she was convinced that it gave her no benefit. Paredrinol was given, but there was inadequate objective evidence of any improvement in one trial. Detailed data of our experience with these two drugs are shown in Tables I and II.

TABLE I

EFFECT OF PAREDRINE HYDROBROMIDE

DATE	DRUG	DOSE (MG.)	TIME	BLOOD PRESSURE LYING	BLOOD PRESSURE STANDING	VERTIGO OR FAINTNESS	REMARKS
3/ 9/43	Paredrine hydrobromide	40	7:00 A.M.				
		20	9:30 A.M.				
		20	12:30 P.M.				
			1:30 P.M.	115/75	60/30(?)	Slight faintness	
			1:40 P.M.	115/75	55/40	Moderate faintness	
	Paredrine hydrobromide	80	1:45 P.M.				
			2:20 P.M.	145/85	110/75		
			2:22 P.M.		110/75		
			2:29 P.M.		120/80		
			2:35 P.M.		110/75		
			4:00 P.M.		110/75		
			4:20 P.M.				Walked to another room
			5:00 P.M.	135/120	60/45	Marked dizziness	
	Paredrine hydrobromide	60	½ hr. before arising				Able to be up better
		40	q. 2 h.				
3/30/43	Paredrine hydrobromide	40	7:45 A.M.				No insomnia
		40	9:45 A.M.				
		40	11:45 A.M.				
			1:30 P.M.	140/85	65/50		
	Paredrine hydrobromide	40	1:45 P.M.				
			2:00 P.M.	135/85	70/50		
			2:30 P.M.		80/50		
			2:35 P.M.	110/80 (sitting)	90/70		
			3:18 P.M.		90/65		
4/ 5/43	Paredrine hydrobromide	80	2:00 P.M.				
			4:45 P.M.	110/80	65/50		
	Paredrine hydrobromide	80	4:46 P.M.				Itching and burning of skin
			5:25 P.M.	128/85	90/70		
			5:35 P.M.		90/60		

Neosynephrin hydrochloride was used next. This drug produced the greatest benefit of any of the vasoconstrictors used. It was impossible to continue to obtain the drug in sufficiently large doses (50 mg.), and it was discontinued because taking five to seven capsules of 10 mg. each

avoidance of any type of strenuous exertion on warm days, and the use of various vasoconstrictor drugs such as have been described by Jeffers, Montgomery, and Burton,[3] Davis and Davis,[10] Korns and Randall,[11] Stead and Ebert,[4] and others.

A patient who presented most of the classical manifestations of orthostatic hypotension has been studied. The effects of the "head-up" sleeping position and of ephedrine, benzedrine, paredrine, paredrinol, neosynephrin, and epinephrine in oil have been observed. With the exceptions to be noted, the procedures and agents proved unsatisfactory.

It was therefore decided to utilize the well-established capacity of desoxycorticosterone to increase blood volume as a method of maintaining an adequate blood pressure in the upright position. The benefits to the patient have been so marked that our observations with this drug form the principal basis for this report.

CASE REPORT

A white woman, aged 48 years, complained of poor health since a pelvic operation eighteen years earlier, and said that her symptoms had been worse since a pregnancy eleven years earlier. Her principal symptoms during all these years had been weakness, increasing dizziness, and a dry skin. For three to four years she had fainted frequently upon assuming the upright position. This was particularly true upon arising and for the remainder of the early morning. Her life for eighteen months to two years before she was seen had been spent primarily in running in a crouched position from one chair to another to avoid extreme dizziness and fainting. In the sitting or recumbent position she was entirely free of the above complaints.

A thorough physical examination was essentially negative, with exceptions to be noted. Subsequently, many attempts were made to discover disease of the nervous system, but no abnormality was discovered. Hypersensitive carotid sinus reflexes of any of the three types were considered and discarded because of inability to reproduce any of her symptoms by vigorous massage over both carotid sinuses. Addison's disease was ruled out because of lack of increased pigmentation, no crises during her years of complaint, and normal blood sugar, sodium, potassium, and chloride values.

The blood pressure was 130/85 with the patient in the recumbent position, and when she assumed the upright position it fell to 80/50; it immediately returned to previous levels upon lying down. After a few minutes in the upright position the blood pressure fell to 50/?, and dizziness was marked. These observations were confirmed on numerous occasions. Not infrequently the systolic blood pressure would fall to 40 mm. Hg, or lower, and she would faint. The cardiac rate sometimes rose to 100 or 110 beats per minute when the patient was in the upright position.

A diagnosis of orthostatic hypotension was made, and attempts at therapy were begun along conventional lines.

TREATMENT

The patient was required to sleep in the "head-up" position for a number of weeks, as recommended by MacLean and Allen, but she insisted that no benefit was derived. Unfortunately, no blood pressure

at intervals of one to two hours made the patient nauseated. Detailed observations are given in Table III. I consider that neosynephrin hydrochloride was beneficial to this patient. It will be noted from the data in Table III that the effects were beginning to decrease markedly in one hour. The dose had to be repeated at no greater than two-hour intervals.

TABLE V. EFFECT OF DESOXYCORTICOSTERONE ACETATE

DATE	DRUG	DOSE (MG.)	TIME	BLOOD PRESSURE LYING	BLOOD PRESSURE STANDING	SYMPTOMS	REMARKS
2/14/44	None		2:17 P.M.	120/90	50/?	Weak and faint	
	DOCS*	10	2:23 P.M.				Felt much improved in 2 hr. for rest of evening
2/15/44	DOCS	10		142/100†	55/?		
2/16/44	DOCS	10					
			3:37 P.M.	152/102			
			3:38 P.M.		105/75		
			3:40 P.M.		95/70		
			3:52 P.M.		80/55		
	DOCS	10	3:55 P.M.				
2/17/44							Felt better than for years, walked across street and back
			2:49 P.M.	156/105	90/60		
	DOCS	5	3:07 P.M.				NaCl 1 Gm.
2/19/44			2:15 P.M.	130/ 88	55/40		
	DOCS	10	2:20 P.M.				NaCl 2 Gm.
2/20/44			11:30 A.M.	150/100	110/75		Noted beneficial effects in 1 hour
	DOCS	10	11:50 A.M.				NaCl 2 Gm.
2/21/44			2:30 P.M.	160/105	120/80		Went shopping (first time in 2 years)
	DOCS	5	2:50 P.M.				NaCl 5 Gm.
2/22/44	DOCS	5		150/ 90	82/60		NaCl 10 Gm.
2/23/44	DOCS	5		155/ 98	130/80		NaCl 10 Gm.
2/24/44	DOCS	5		154/100	130/84		NaCl 15 Gm.
2/25/44	DOCS	5		165/105	120/80		NaCl 15 Gm.
2/26/44	None			165/110	110/80	Severe headache sitting or lying	
2/27/44	None			166/110	110/82		NaCl 15 Gm.
2/28/44	None				110/80		NaCl 15 Gm.
4/15/44	DOCS	5	q. 5 to 7 days	125/80†	100/70	None	NaCl 15 Gm.
4/20/44	DOCS	5	1:40 P.M.	122/82†			
			1:41 P.M.		90/66		
			1:46 P.M.		80/64		Continued standing
4/25/44	DOCS	5	1:30 P.M.	142/100†			
			1:31 P.M.		90/70		NaCl 20 Gm.
			1:37 P.M.		76/58		Continued standing

*DOCS = desoxycorticosterone acetate.
†Sitting.

TABLE II

EFFECT OF PAREDRINOL AND PAREDRINE

DATE	DRUG	DOSE (MG.)	TIME (P.M.)	BLOOD PRESSURE		DIZZINESS OR FAINTNESS	REMARKS
				LYING	STANDING		
5/11/43	None			90/60	45/? to 0		Fainted
	Paredrinol	60	1:45				
			2:20	85/60			
			2:55	100/70			
			2:59	35-40/?	sitting		Faint
	Paredrine	60	3:00				
			3:55	100/70			
			3:57		50/?		
			5:20	140/90	75/55		

TABLE III

EFFECT OF NEOSYNEPHRIN HYDROCHLORIDE

DATE	DRUG	DOSE (MG.)	TIME (P.M.)	BLOOD PRESSURE		DIZZINESS OR FAINTNESS	REMARKS
				LYING	STANDING		
6/29/43	None		1:33	110/70	50/?	Very dizzy	
	Neosynephrin hydrochloride	50	1:37				
			2:55	140/92	100/70	No symptoms	
			2:58		85/60	No symptoms	Walked down hall
			3:00		90/60		
			3:02		90/60		
	Neosynephrin hydrochloride	50	3:03				
			4:00	145/90			
			4:01		110/80		
			4:03		92/65		
			4:05		70/55		
			4:07		70/55	No symptoms	Feels fine Unable to continue to get 50 mg. capsules

TABLE IV

EFFECT OF EPINEPHRINE IN OIL

DATE	DRUG	DOSE (C.C.)	TIME (P.M.)	BLOOD PRESSURE		SYMPTOMS	REMARKS
				LYING	STANDING		
10/1/43	Epinephrine in oil I. M.	0.4	1:58				
			2:03	105/70	55/40	Dizzy	
			2:51	160/90	100/60		
			2:53		80/55		
			2:54		80/55		
			2:56		70/50		Walking around
			3:02		105/70		Walking
			3:07		100/70		Walking
			3:08		100/68		Standing
			4:50		70/55	No symptoms	
			4:56		65/45		Rubbed arm 2 min.
			4:58			Palpitation	
			5:00		120/80		
			5:02		120/80		No symptom since original dose

chloride for about twelve hours, another 5 Gm. of sodium chloride were added, and the total of 20 Gm. were divided equally through the twenty-four hours. Since the institution of this regime of salt, she feels much stronger in the mornings than had been the case previously.

It has been demonstrated on frequent occasions, as can be seen from the data in Table V, that the administration of salt alone is inadequate to maintain the blood pressure at normal levels in the upright position. This is significant in view of the claims of MacLean, Allen, and Magath[8] that added salt was of value in the management of orthostatic hypotension.

Subcutaneous implantation of pellets of desoxycorticosterone according to the method of Thorn[12] has been considered. The patient has hesitated because of the simplicity of the present management.

SUMMARY AND CONCLUSIONS

A case of orthostatic hypotension is reported, and detailed objective evidence of the value of various therapeutic agents is presented and briefly discussed.

Attention is called particularly to the therapeutic value of small doses of desoxycorticosterone acetate in oil by intramuscular injection, in conjunction with an increased oral intake of sodium chloride in orthostatic hypotension.

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ADDENDUM

This patient has been taking desoxycorticosterone for slightly more than a year. For many months, 5 mg. of desoxycorticosterone, plus 15 to 20 Gm. of salt daily, continued to give her satisfactory relief with the exception of the early morning hours. For this reason, three pellets of Percorten, 125 mg. each, were implanted cautiously at about three-to four-week intervals. Since the implantation of these pellets it has been possible for this patient to get along on an injection schedule of 5 mg. twice weekly. We have found this schedule the most satisfactory one that we have tried up to the present time.

TABLE V—CONT'D

DATE	DRUG	DOSE (MG.)	TIME	BLOOD PRESSURE		SYMPTOMS	REMARKS
				LYING	STANDING		
4/29/44	DOCS	5	3:30 P.M.	145/102†			NaCl 20 Gm.
			3:31 P.M.	154/102†			NaCl 20 Gm.
			3:31 P.M.				Stood up
			3:32 P.M.		105/84		NaCl 20 Gm.
			3:33 P.M.		100/84		Started walking
			3:37 P.M.		94/70		Continued walking
5/ 4/44	DOCS	5					NaCl 20 Gm.
5/ 9/44	DOCS	5					NaCl 20 Gm.
5/13/44	DOCS	5	4:22 P.M.	142/100†	(5 min.)		Stood up
			4:22½ P.M.		120/88		NaCl 20 Gm.
			4:24 P.M.		112/90		Started walking
			4:27 P.M.		95/68		NaCl 20 Gm.

No central nervous system symptoms were ever observed. It is unfortunate that it was not commercially available in dosage units adequate for the treatment of orthostatic hypotension.

Epinephrine in oil proved to be of definite benefit to this patient, as shown by the detailed observations in Table IV. The injection was given in the arm. The data show that the effects began to decrease within one hour after injection. Walking, however, increased the blood pressure of the patient in the upright position. It may also be noted that vigorous massage of the injection site produced further beneficial effect as long as three hours after the injection.

Epinephrine in oil was continued for two months with benefit. It became necessary to discontinue it because of extreme tissue reactions at the site of injection. I believe from this limited experience that epinephrine in oil deserves further consideration in the treatment of orthostatic hypotension.

The capacity of desoxycorticosterone to increase the blood volume was considered. It was thought that the blood volume could be safely raised by this method far enough to prevent the fall of the blood pressure to levels which would produce symptoms. Our experience with this drug has been most gratifying. The patient has returned to all the usual activities of her life for the first time in many years.

Desoxycorticosterone acetate in oil was injected intramuscularly in conjunction with sodium chloride by mouth. In addition to its complete effectiveness, it has the further comparative advantage that it need be administered only every five to seven days, whereas the vasoconstrictor drugs must be taken every one to three hours daily. The detailed data are presented in Table V.

The possible dangers of desoxycorticosterone must be emphasized. These dangers have been reported repeatedly. It is essential that this very potent substance be employed with rigid control of the blood pressure and weight. This is particularly essential when desoxycorticosterone is employed in conjunction with added sodium chloride, as we have done, to reduce the dosage of desoxycorticosterone to a minimum.

It will be noted from the data in Table V that severe and persistent headaches occurred as a result of the elevated blood pressure during the period in which the dosage level was being established.

As a general rule, the patient felt much stronger in the afternoons. Believing this morning weakness might be due to failure to take sodium

reported as "positive for hemosiderin crystals." He was sent to San Francisco, and entered Stanford Hospital Oct. 16, 1942.

Physical Examination.—He was a thin young man, with a slaty, gray, dirty, diffuse pigmentation of the skin, most prominent on the backs of the hands, on the face, and in the skin creases. There was no obvious pigmentation of the mucous membranes. The distribution of hair was feminine in type. Examination of the eyes, ears, nose, and throat showed nothing remarkable. A few moist râles could be heard in the right lung. The heart was enlarged to the left; the heartbeat was regular, with a rate of 44. In early diastole an extra sound, such as might be associated with auricular systole, was heard. The sounds otherwise were not remarkable. The blood pressure was 110/80. The abdomen was moderately distended, with signs of ascites. The liver was firm and slightly tender, and extended below the umbilicus. The spleen was not palpable. There were no obvious penile or testicular abnormalities. The legs and thighs were the seat of massive, soft, pitting edema. Neurological examination showed nothing remarkable.

Laboratory Data.—The erythrocyte count was 3.63 million per cubic millimeter, with a hemoglobin content of 13.5 Gm. (75 per cent Sahli); the leucocyte count was 8,400 per cubic millimeter. The blood Wassermann and Hinton reactions were negative. The urine was normal. The fasting blood sugar was 256 mg. per cent. The blood urea on entry was 42 mg. per cent, and the plasma chlorides were 544 mg. per cent (as sodium chloride). The direct van den Bergh was negative: the indirect was 2.4 units, with an icterus index of 19. The serum proteins (Kagan falling drop method) were 5.7 grams. A bromsulfalein dye excretion test (2 mg. per kilogram) showed 10 per cent retention of the dye in the serum after thirty minutes. The venous pressure (five days after entry) was 18 cm. of saline solution as measured in the antecubital fossa; the arm-to-tongue circulation time (with 20 per cent Decholin) was sixty seconds. The vital capacity was 3.3 liters.

Roentgenologic examination of the abdomen and skull revealed no abnormalities. A roentgenogram of the chest on Oct. 16, 1942, showed marked enlargement of the heart (Fig. 1). Electrocardiograms taken from Oct. 19, 1942, until Nov. 3, 1942, showed complete auriculoventricular block, with low voltage ventricular complexes, abnormal T waves, and right axis deviation (Fig. 2).

A skin biopsy showed marked deposition of iron around the sweat glands.

The diagnosis of hemochromatosis was made, although it was thought that this did not explain everything; the possibility that the ascites and massive edema were secondary to cirrhosis of the liver was entertained, but, because of the cardiac abnormalities, the likelihood of heart failure was considered more probable. The hyperglycemia was of the sort usually seen in hemochromatosis, and will be dismissed here with the statement that his diabetes was adequately controlled with a diet of 270 Gm. of carbohydrate, 90 Gm. of protein, 60 Gm. of fat, and 40 units of protamine zinc insulin daily.

Digitalis was administered with an initial dose of 0.6 Gm., then 0.4 Gm. on the following day, 0.2 Gm. daily for the next six days, and 0.1 Gm. daily, thereafter. He was given 0.5 c.c of mercupurin, and 1.5 c.c. two days later. There was prompt and impressive diuresis, with a weight loss from 70.5 kilograms to 57.1 kilograms in six days.

Clinical Reports

HEMOCHROMATOSIS WITH COMPLETE HEART BLOCK

With a Discussion of the Cardiac Complications

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ALTHOUGH a huge literature on hemochromatosis has accumulated since Trousseau's[1] description little has been said in the American and English writings on the cardiac complications of this disease. Our interest in the subject was aroused by the following case.

CASE REPORT

A. Mc. (S.U.H. 216076), aged 35 years, entered the hospital Oct. 16, 1942, complaining of fatigability, weakness, impotence, loss of libido, and pigmentation of the skin for the preceding two or three years. His past history was not remarkable; there was no story suggestive of rheumatic fever, syphilis, or chronic alcoholism. His present illness consisted of a group of signs and symptoms which he thought began after an attack of "flu" in February, 1940; after this he began to notice that he tired easily, that normal libido was absent, and that in the succeeding year his skin gradually became darker; he thought there had been some loss of hair from the arms and legs. By the summer of 1941 he felt better except for impotence and fatigue. In November, 1941, and again in January, 1942, he had two ten-day febrile periods, with fever to 105° F. The nature of these attacks was not clear. As a sequel to each, there was an increase in general weakness and malaise. In addition, he said that his heart rate fell from 60 to 34 in January, 1942, and that it had never been faster thereafter. Both of the febrile illnesses were treated with sulfonamides. He made a partial recovery, but, in the spring of 1942, noticed that he was short of breath on exertion and that he had occasional precordial pains which were not made worse by exertion. In July, 1942, on a mountain trip (elevation 11,500 feet), he became acutely ill, with severe dyspnea, marked weakness, and massive swelling of the legs and abdomen. Rest in bed and diuretics brought about a remission of symptoms. However, he felt weak ever after, and his weight declined from 170 to 135 pounds. About three weeks prior to entry he noticed frequency of urination and excessive thirst; on Oct. 7, 1942, he was admitted to the Santa Monica Hospital "in diabetic coma with hyperglycemia, glycosuria and ketonuria"; his diabetes was controlled fairly easily, and he was put on a maintenance dose of 10 units of regular insulin, morning and evening. Examinations of the urine at that hospital were

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Received for publication Oct. 1, 1943.

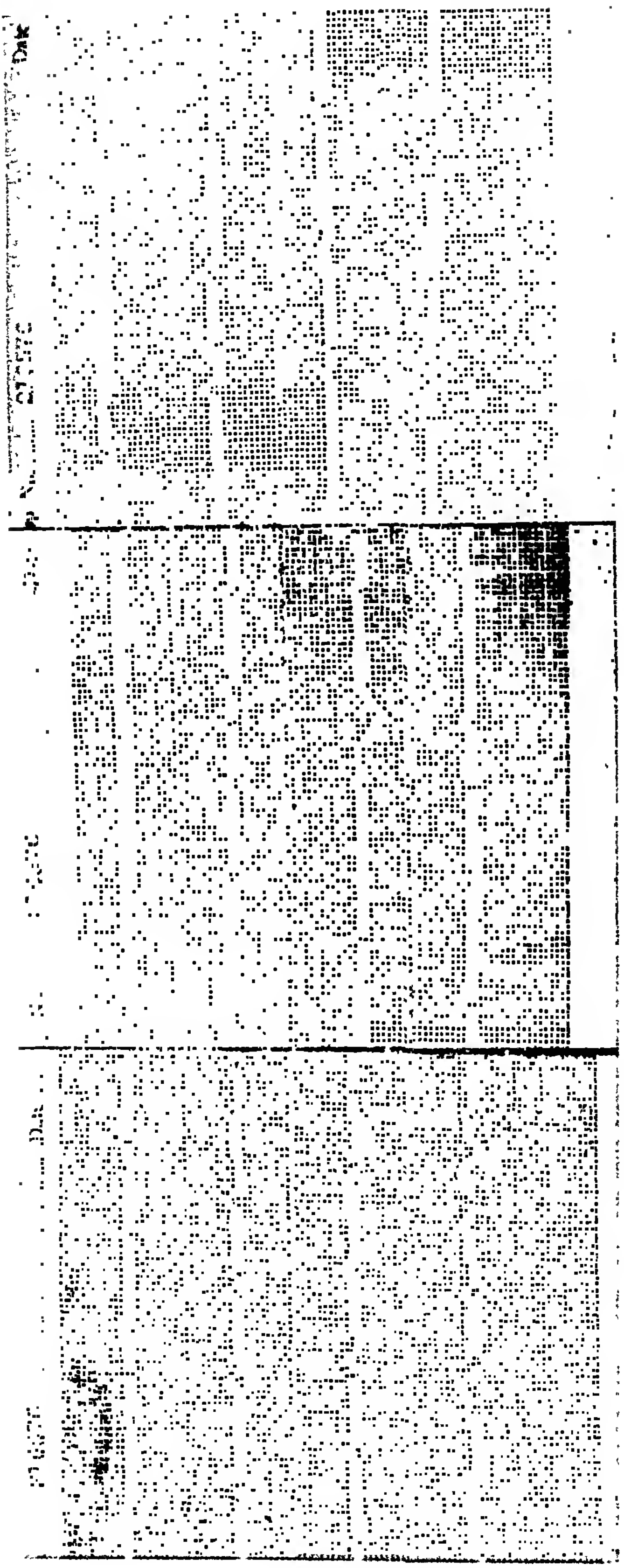

Fig. 2.—Electrocardiograms on October 19, October 24, and November 3.

Along with this there was complete disappearance of the edema and ascites. The liver became much smaller, as did the heart (Fig. 3). The venous pressure fell to 5 cm. of saline solution, and the arm-to-tongue circulation time to 21 seconds; the arm-to-lung circulation time (done with ether) was 16 seconds. The direct van den Bergh was negative; the indirect was 0.68 units; the icterus index was 6 (Nov. 3, 1942). The electrocardiographic studies were interesting, in that, with the administration of digitalis, the auricular rate fell from 103 to 71, whereas the ventricular rate fell slightly, from 44 to 36.

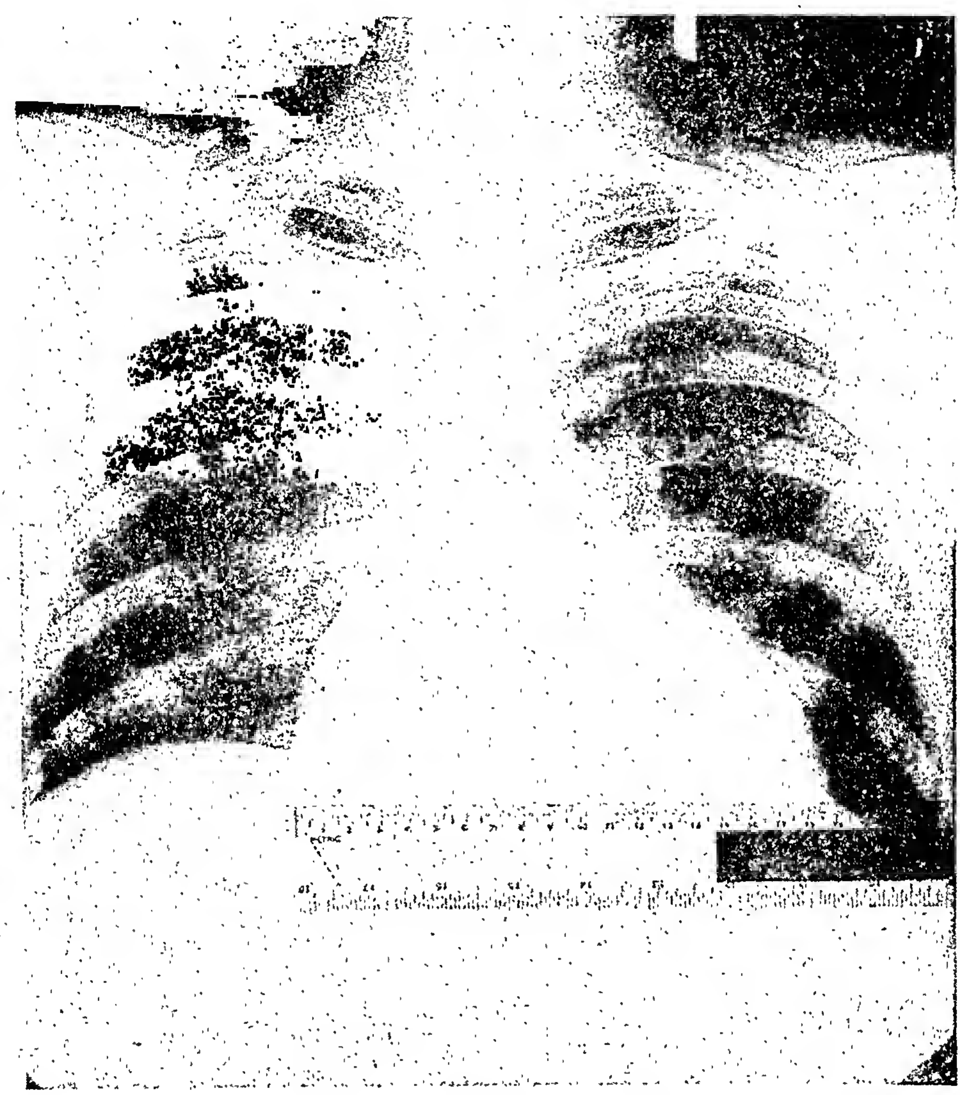

Fig. 1.—Roentgenogram of the heart before treatment.

The patient was dismissed on Nov. 7, 1942; he was in fair condition, was taking digitalis in a dose of 0.1 Gm. daily, and had no signs of heart failure. In January, 1943, word was received that he had died. Dr. J. P. Sampson, his personal physician, and Dr. A. A. Kosky sent some pieces of tissue to the Department of Pathology for study. There were no gross abnormalities of the heart valves or coronary vessels. Examination of the sections showed, in general, the characteristic changes of hemochromatosis, with iron deposition in the heart, liver, adrenals, pancreas, and, to a less extent, in the kidneys and lungs. Of special interest were the heart specimens. These showed localized areas of atrophy in the myocardium. The muscle fibers contained

dark brown pigment granules, and special stains showed numerous fat droplets. There was considerable variation in the size of the individual fibers; some terminated in threadlike processes. There were numerous broad spaces between fibers, containing fibroblasts and pigment-filled macrophages (Fig. 4). It was the opinion of Dr. Cox and his associates in the Department of Pathology that these changes could be interpreted as evidence of injury to the heart. The sections did not contain the bundle of His, so that the exact anatomic cause of the heart block is not known.

In reviewing the histories of about a dozen cases of hemochromatosis which have been seen at Stanford Hospital, none was similar to the one described here. In cases with autopsy reports there was no mention of myocardial fibrosis, although the sections in some showed as much iron as did this patient's heart.

DISCUSSION

This patient presented the usual features of hemochromatosis, plus heart failure with complete auriculoventricular block. In a search for data on the cardiac complications of hemochromatosis, the standard English textbooks on heart disease were examined, but no pertinent reference was found. Sheldon,[2] in his thorough monograph, makes the statement that "several cases have died from heart failure," but has little further comment. Only four[3-6] adequate reports on heart failure and hemochromatosis could be found in the English literature, and, of these, only two[3, 4] emphasize the heart failure. The first of these[3] concerned a man, 54 years of age, and the second[4] described three cases of hemochromatosis in which the heart was abnormal. These patients were men, aged 59, 43, and 21 years, respectively. The last case was comparable to ours, for not only was heart failure present, but it was associated with complete auriculoventricular block, and at one time with auricular flutter.

In contrast to the few English reports, there is a large French literature on cardiac disorders in hemochromatosis.[7-19] The authors describe fully some twenty cases of heart failure in young adults with "bronzed diabetes." The most complete discussion is that of R. de Vēricourt.[19] It is the opinion of the French that there is a symptom complex, "syndrome endocrino-hepato-cardiaque," in which there are all of the common manifestations of hemochromatosis, plus heart failure; this occurs almost exclusively in young adults. The French authors discuss this syndrome in great detail, and seem familiar with it as an entity.

Counting the four cases in the English literature, twenty-five case reports were, reviewed. All but three of the patients were under 45 years of age; of the three, two were 54 years old and one was 59 years old. There were two cases[5, 17] in women, aged 34 and 18 years, respectively. Cardiac arrhythmias were not uncommon. There were two cases[4, 5] with auricular fibrillation, one with auricular tachycardia[5] and, interestingly enough, two besides our own with complete auriculo-

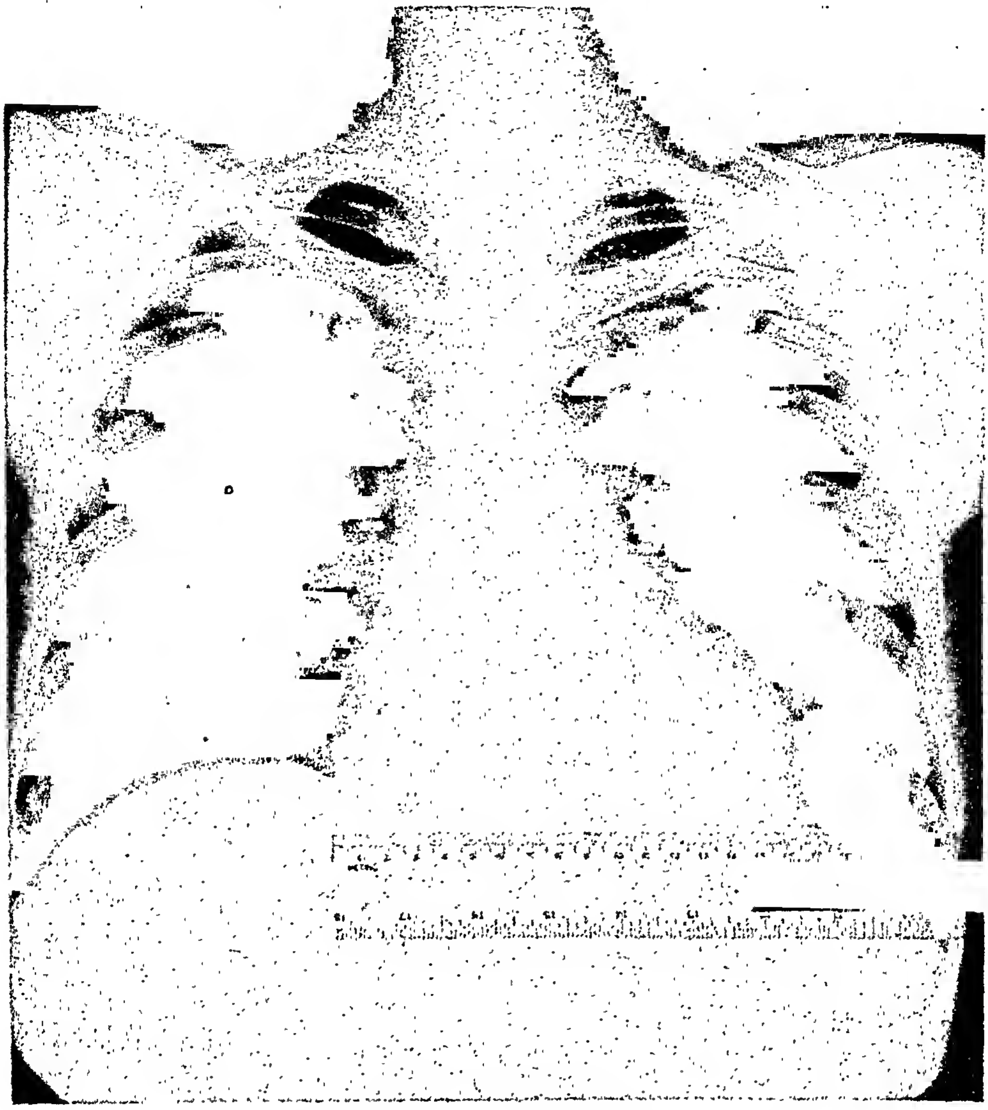

Fig. 3.—Roentgenogram of the heart after treatment.

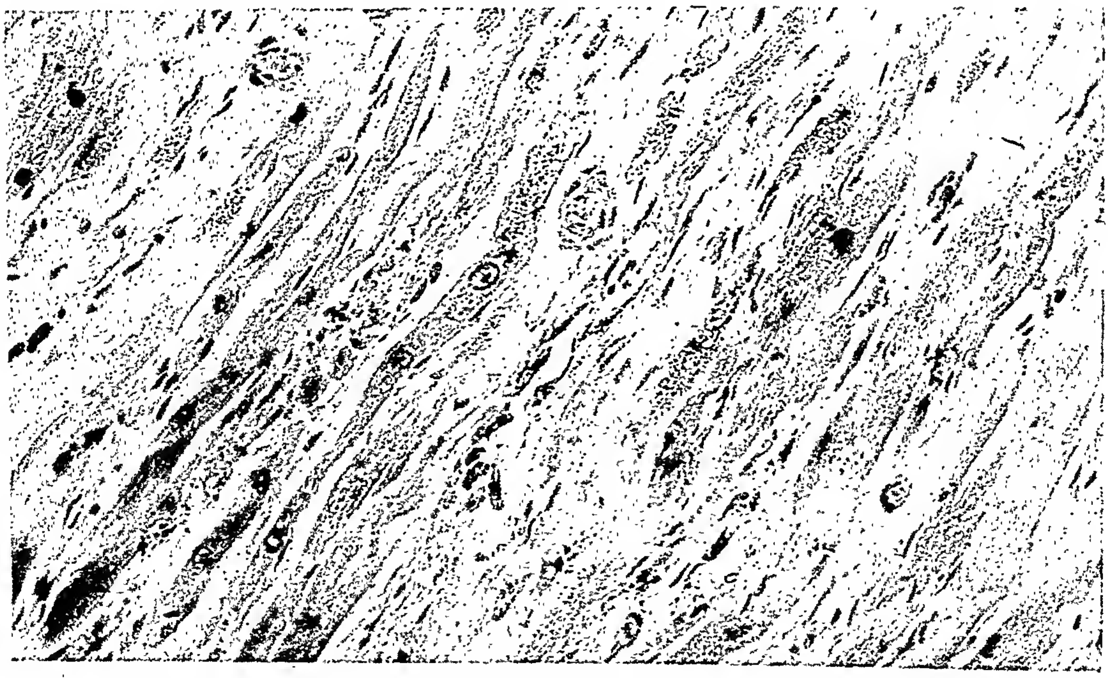

Fig. 4.—Microscopic sections of the heart muscle, showing pigmented granules in the fibers.

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ventricular block.[4, 10] The remainder apparently had regular sinus rhythm, although, in two,[6, 12] frequent premature beats were noted. In three cases[9, 10, 12] "low voltage" in the electrocardiogram was reported. Two patients[5, 6] complained of severe, tearing, chest pain. Subsequent autopsy revealed no coronary artery disease or evidence of infarction in either case. The response to therapy could not be predicted from a study of the cases. Some patients[14] failed to improve whereas others improved markedly, only to fail again shortly. One patient[10] was followed for seven years. The average duration of life after the development of heart failure was about nine months. The cause of these cardiac complications is not known. The French writers are convinced that they are not the result of local damage to the heart by iron. They emphasize the lack of fibrosis and absence of derangement of myocardial architecture in the cases they studied histologically. They attribute the heart failure to some generalized metabolic disorder whose nature is uncertain. On the other hand, Blumer and Nesbit[3] and Maling and Riley[6] demonstrated extensive fibrosis in the heart muscle in their cases. Kerr and Althausen[4] apparently feel that local damage to the heart is important, for they speculate upon the possibility that heart failure may be seen more frequently in hemochromatosis since the patients are enabled to live longer by the use of insulin.

In our own case the heart muscle did show some signs of injury that could have played a part in the production of heart failure. The presence of auriculoventricular block is evidence of local tissue damage. Unfortunately, there are no adequate series of cases of hemochromatosis with and without heart failure which would enable one to correlate clinical data with anatomic observations. Sheldon[2] and Butt and Wilder[20] describe heavy iron pigmentation of the heart muscle, but there is no mention of fibrosis or scarring.

CONCLUSIONS

A case of hemochromatosis with heart failure and complete heart block is described.

The importance of the cardiac complications, which are emphasized in the French literature, has not been sufficiently stressed in the English writings on hemochromatosis.

The mechanism of the production of cardiac failure and disturbances of rhythm in hemochromatosis is discussed.

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of digitalis, his symptoms worsened progressively until he was admitted to the hospital in a critical condition. As far as could be ascertained, digitalis had been stopped on Oct. 18, 1942.

Physical examination revealed an orthopneic, cyanotic, grossly edematous man, seriously ill. The tongue was dry. The neck veins were distended and pulsated irregularly. Numerous râles were present throughout both lungs. The heart was markedly enlarged; the apex beat was diffuse. Auricular fibrillation was present: the apical rate was 120, and the radial, 86. No murmurs were heard, but occasional accentuation of the muffled heart tones aroused the suspicion that ectopic beats were present. The blood pressure was 145-150/110-120. The abdomen was distended, and the edge of the liver was firm, tender, and 2 inches below the costal margin. Although no free fluid was demonstrated in the abdomen, there was marked edema of the abdominal wall, extremities, and scrotum. His weight was 210 pounds.

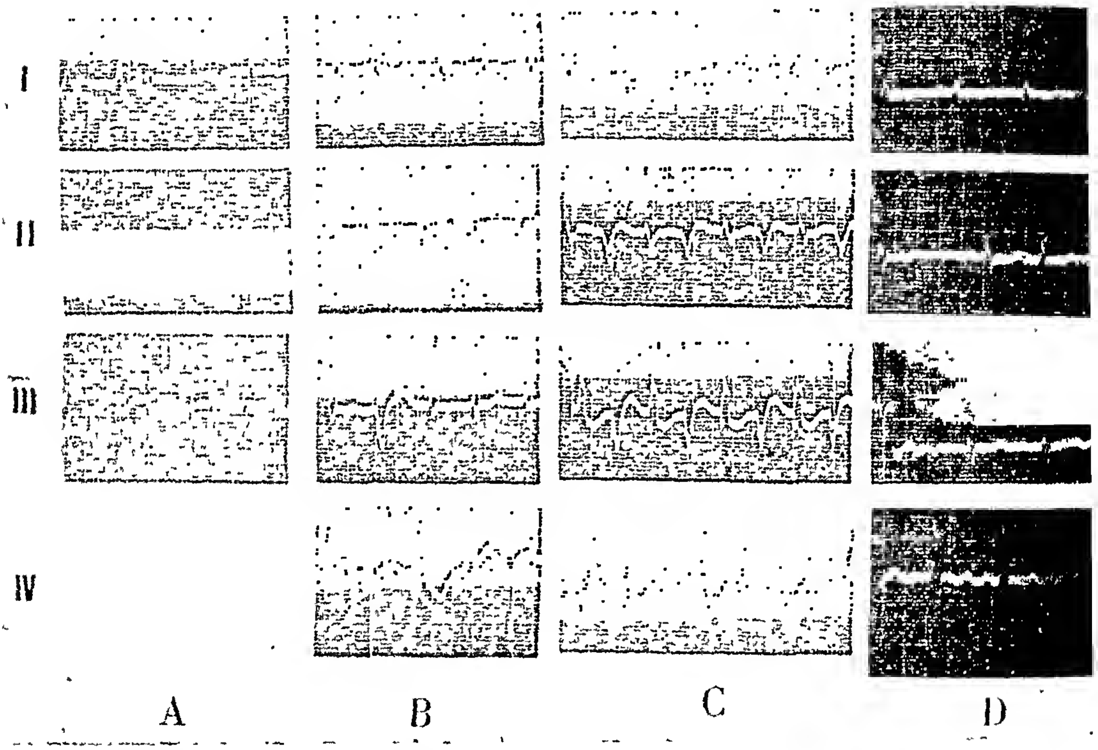

Fig. 1.—*A* shows the extremity leads in 1936; *B* shows four leads upon admission to hospital Nov. 20, 1942; *C* shows electrocardiographic appearance at the height of the bidirectional paroxysmal ventricular tachycardia; *D* shows the electrocardiogram in June, 1943.

The electrocardiogram (Fig. 1, *B*) showed auricular fibrillation with a ventricular rate of approximately 130, ectopic ventricular systoles, left axis deviation, low voltage of the QRS complexes, and flattening of the T waves such as occurs with serious myocardial damage. The teleoroentgenogram (Fig. 2, *A*) showed the following measurements: M R* = 7.5 cm., M L† = 14.6 cm., and transverse diameter of chest, 30.6 centimeters. According to the Ungerleider and Clark[7] method, the theoretical value for the total diameter should not exceed 123 millimeters.

*M R = midline to right border
†M L = midline to left border.

BIDIRECTIONAL PAROXYSMAL TACHYCARDIA: TOXICITY OF DIFFERENT CARDIAC GLYCOSIDES

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INTRODUCTION

PAROXYSMAL ventricular tachycardia is rare,[1,2] and the bidirectional variety is even rarer.[3,4] We have obtained records of the beginnings and endings of a number of long paroxysms. Since only a fraction of the published curves register these onsets and terminations, we feel justified in reporting this case, even though numerous controversial points concerned with the origin and mechanism remain unsolved. Clinically, the solution of these points can be approached only by analysis of the electrocardiographic pattern of a large number of tracings, including the onsets and terminations.

The role of digitalis in the causation of paroxysmal ventricular tachycardia is well known. In our case we demonstrated an apparently selective toxic sensitivity to *Digitalis purpurea* which was in marked contrast to the beneficial effect of strophanthin in controlling failure; the patient tolerated *Digitalis lanata,* which has maintained compensation.

This case is also interesting because of the length of life (twenty-seven months) after the attack, in view of the serious prognosis, if not terminal condition, that these paroxysms usually portend.

CASE REPORT

C. S., a 68-year-old construction engineer, was admitted to the Illinois Masonic Hospital Nov. 20, 1942. The family history revealed serious cardiorenal vascular disease on both sides; the patient was the only survivor. His past history revealed long and hard years of work. In 1935 (at the age of 61 years) he had an attack of pain in the chest radiating into the shoulders. After two weeks in bed he returned to work and remained under medical supervision, receiving varying and unknown amounts of digitalis. In 1936 an electrocardiogram showed auricular fibrillation and evidence of severe myocardial damage (Fig. 1, *A*). In 1941 (at the age of 67 years), he had what was possibly a pulmonary embolus after a hemorrhoidectomy. This delayed his convalescence ten days. In May, 1942, he had several boils which were treated surgically and successfully. However, by June he was short of breath, he started to cough, and he noted swelling of the ankles. In spite of numerous variations in the dosage, type, and mode of administration

Read by title at the Sixteenth Annual Meeting of the Central Society for Clinical Research, Chicago, Nov. 5, 1943.

Received for publication Nov. 1, 1943.

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ologically (Fig. 2, *B*), there was a decrease in the pulmonary congestion and in the size of the heart shadow. The measurements were: M R = 4.9 cm., M L = 12 cm., and total diameter of the chest, 31.4 centimeters. He was discharged from the hospital in a greatly improved condition on Feb. 14, 1943, seventy-six days after admission.

At home the *Digitalis lanata* was reduced to 1 cat unit every second or third day, and the quinidine discontinued. The patient continued to gain in strength. In June the *Digitalis lanata* was stopped, and, although his weight did not change, the apical rate increased almost 20 beats per minute. Therefore, the small doses were resumed. The electrocardiogram (Fig. 1, *D*) showed a continuation of the low voltage and evidence of myocardial damage. Only occasional ectopic beats were noted.

The patient is up and about. Occasionally, he has even returned to business. During the entire period he has been maintained upon a modified acid-ash, low-sodium diet, with 6 to 9 Gm. of ammonium chloride daily. At no time during his illness did numerous blood chemical values deviate from the normal.

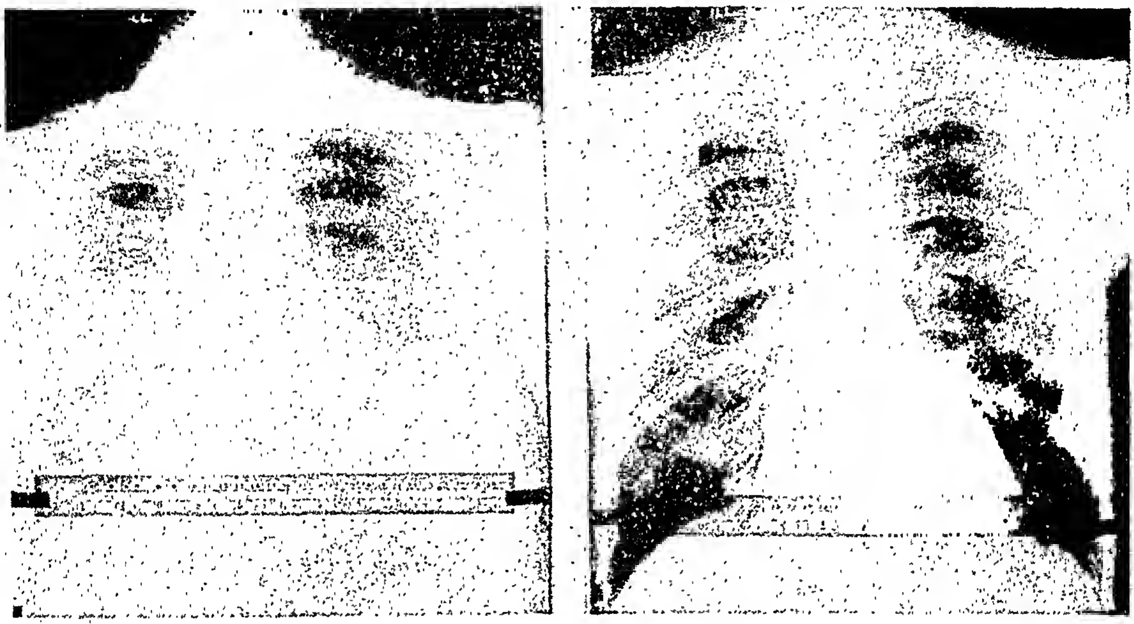
COMMENT

This patient was both interesting and instructive. It would seem that he had myocardial infarction in 1935, and that this caused the auricular fibrillation. The electrocardiogram in 1936 (Fig. 1, *A*) substantiates this diagnosis. He was symptomless, however, until the series of furuncles developed in 1942, after which cardiac decompensation appeared. It is not known whether there were attacks of ventricular tachycardia previous to his hospitalization. Failure, however, increased, and digitalis must have been suspected as a cause because the drug had been discontinued.

After admission, the increasing degree of congestive failure while he was in bed, the auricular fibrillation with rapid ventricular rate, and assurance from the family physician and the patient's own records that no digitalis had been received for five weeks prompted the administration of digitalis. We were not in possession of the 1936 electrocardiogram at the time, and we felt that the auricular fibrillation was a recent development, coinciding with the decompensation. *Digitalis purpurea* administration led to attacks of ventricular tachycardia which ceased when the drug was discontinued, and reappeared upon resumption of the drug. Quinidine was then given, despite the apparently diffuse, serious myocardial lesion, and without much hope of either establishing normal rhythm or having much effect upon the ventricular contractions.[6] The ventricular rate remained rapid, and there was no effect upon the number of ectopic beats, the Cheyne-Stokes breathing, or the edema.

Unequivocally, all of the indications for digitalization remained the same. Oettel,[7] investigating the so-called "paradoxical action" of the digitalis glycosides (increase in the sinus rate and appearance of ectopic beats), pointed out the lesser toxicity of the strophanthin series. In this respect, the lanata glycosides have been considered superior to the purpurea glycosides.[8] Accordingly, we administered strophanthin in

The patient's weight while he was at rest in bed increased 10 pounds in two days. Since he had received no digitalis for thirty-five days, he was given 12 cat units of *Digitalis purpurea* on November 22, 4 cat units on November 23, and 6 cat units on November 24, all in divided doses, when the first paroxysm of alternating ventricular tachycardia was discovered (Fig. 1, *C*) and the digitalis was stopped. These attacks subsided within two days, but the edema increased and Cheyne-Stokes breathing became more marked, with apneic periods lasting almost sixty seconds. The patient's condition was considered hopeless. Oxygen was administered constantly. Mercupurin in ⅓ c.c. or ½ c.c. doses was given almost daily with unpredictable effect. Because of the patient's poor condition and continued auricular fibrillation, it was decided to administer digitalis in smaller doses in an attempt to slow the rapid ventricular rate. Accordingly, 1 cat unit was given at approximately twelve-hour intervals from November 29 until December 5, when attacks of paroxysmal tachycardia similar in type to that shown in Fig. 1, *C*, recurred.



A. *B.*

Fig. 2.—Shows the teleoroentgenogram taken; *A*, upon admission, and *B*, upon discharge.

Quinidine sulfate was started (3 grains) on December 11. This dose was increased to 9 grains on December 12, 12 grains on December 13, and 18 grains on December 14 without appreciable improvement. On December 15, this dosage was reduced to 9 grains daily, and 0.125 mg. of strophanthin was administered intravenously. From December 16 to December 23, strophanthin was given in a dose of 0.25 to 0.50 mg. daily. At this time the patient developed an upper respiratory infection (pulmonic infarction?), and his temperature was elevated. In spite of this, he improved, as was shown by a slowing of the ventricular rate and a diminution in the pulse deficit. At this time he was receiving 6 grains of quinidine and 0.125 mg. of strophanthin, at first daily and then intermittently, and occasional ½ c.c. doses of mercupurin; this completed the dehydration process. On January 12, the patient weighed 148 pounds, i.e., he had lost 72 pounds. On January 18, *Digitalis lanata* (1 cat unit daily) was substituted for the strophanthin. Roentgen-

(Fig. 1, *B*, Lead I). Whether this difference is due to a digitalis effect cannot be stated with certainty. The rate is slower and the possibility of a fusion beat has to be considered. In Fig. 3, *B*, the paroxysm begins with a premature beat, the coupling time and contour of which are similar to the one in Fig. 3, *A*. The main deflection of the second complex is directed downward. The next five complexes show irregularities in shape, direction, and rate. These variations may be due to (a) origin of the stimulus in the ventricles from multiple foci; (b) origin from one focus with aberrant pathways; or (c) fusion (interference)[14, 15] phenomena. After the first seven complexes, the regular bidirectional tachycardia evolves, as is shown in Fig. 1, *C*. It is to be noted that there is a definite difference between the shape of the upwardly directed complexes at the onset and in the middle of the paroxysm. In *C*, the end of a paroxysm is shown. The rate slows gradually, just as it increased speed gradually after the onset. After the first complex shown, irregularities appear, i.e., two consecutive upwardly directed complexes are present, in this instance partly obscured by the standardization. The eighth complex comes "prematurely," is aberrant, and is followed by a "compensatory pause" (the distance between the seventh and ninth complexes, measured from the point where the trace leaves the base line, is very close to the distance between the fifth and seventh) before the next upwardly directed deflection occurs. This pause is followed by a blunted complex which is followed by a still longer pause, roughly equal in time to that noted in Fig. 3, *G* and *J*. A bizarre, widened complex (number 11) may represent a fusion beat. After a definite supraventricular complex, a pair of alternating extrasystoles occurs, the first of which is upright, after which the mechanism returns temporarily to auricular fibrillation.

In Lead II of Fig. 3, a single premature ventricular systole is shown in *D*, and a similar complex is seen in E, followed closely by another premature beat of a different configuration; these are the same two forms that appear to initiate the paroxysm in *F*. The coupling time of this extrasystole is different in *D*, *E*, and *F*. In *F*, the third complex is broadened, is distinctly downward, and is similar in form to that noted at the height of the paroxysm. After two alternating complexes the form changes abruptly and completely to unidirectional tachycardia with a rate of approximately 150 per minute. Near the end of this paroxysm (not shown in Fig. 3) the rate gradually slowed, the shape gradually returned to that of the third and fifth complex, and the paroxysm ended with a somewhat premature contraction, suggesting interference, after which the supraventricular rhythm was restored. This unidirectional variation was unusual, and was recorded upon one occasion only. The typical alternating complexes in Lead II may be seen in Fig. 1, *C*. In Fig. 3, *G*, a slight slowing of the tachycardia may be observed, and two downwardly directed complexes occur which herald the end without further irregularities.

doses increasing from 1/8 to 1/2 mg. daily; this was well tolerated, and improvement was steady and gratifying. We are unable to say that a beneficial synergism existed between the quinidine and strophanthin, although we realize the possibility. When the patient had improved sufficiently, *Digitalis lanata* was administered with gratifying results. This was done to avoid continuous intravenous therapy.

Throughout the entire period of observation, we were impressed by the lack of relationship between the amount of mercurial diuretic given and the subsequent urinary output. Small doses, of 1/3 c.c., and even less, are safer and are superior[9] to large doses. The total urinary output after eight 1/4 c.c. doses, given upon alternate days, invariably exceeds the response obtained from 2 c.c. given in one dose.[10] The important feature is the state of the circulation, which was stressed by earlier writers upon the subject. In our case ammonium chloride was given throughout the entire hospitalization in doses of 6 to 9 Gm. daily.[11] During the first period of digitalization a fair but unreliable diuretic effect of the mercurial was observed, quite independent of the amount injected and with noticeable ineffectiveness during the periods of the paroxysms. The diuretic effect was poor when the mercurial was given with quinidine. Simultaneous or previous administration of aminophyllin by mouth or intravenously was without effect.[12] During the time of the first doses of strophanthin, the effect was poor; it was adequate and reliable, depending on whether an improved circulation was maintained by strophanthin or *Digitalis lanata.*

Ventricular tachycardia is a serious disturbance, and the bidirectional type is considered to be fatal.[13] The prognosis varies with the seriousness of the underlying cardiac lesions. In spite of the enlargement and dilation of the heart, possible pericardial effusion, myocardial infarction, coronary sclerosis, hypertension, and auricular fibrillation, this patient may still be in Class III according to the Criteria Committee of the New York Heart Association,[5] twenty-seven months after the attacks of tachycardia.

The electrocardiographic appearance of the paroxysm at the height of the attack is shown in Fig. 1, *C,* during which regularly alternating complexes may be observed. The rate approximated 160 per minute.

Fig. 3 shows the electrocardiographic appearance between the paroxysms (*A, D, E, H,* and *K*), the onsets of the paroxysms in four leads (*B, F, I,* and *L*), and the endings in the extremity leads (*C, G,* and *J*).

The auricles are fibrillating, and, in Lead I, the ventricular rate (Fig. 3, *A*) is about 100 per minute, which is slower than was noted upon admission (Fig. 1, *B*). The QRS complexes are of low voltage and the T waves are practically isoelectric. This supraventricular mechanism is interrupted by an ectopic systole of right ventricular origin, the coupling time of which cannot be measured exactly. This ectopic beat is similar to, but is not exactly the same as, the one observed upon admission

In Lead III (Fig. 3, *H*) a downwardly directed premature systole is shown. This is similar in contour to the extrasystole noted in Lead III (Fig. 1, *B*), taken upon admission, the fifth complex in *I*, and the downwardly directed complex during the height of the paroxysm. In *I*, the first deflection is an extrasystole similar to the one which initiates the paroxysm. In this onset no such major irregularities occur as were noted in *B* and *F*, although, in other strips, these were noted frequently. Toward the end (*J*) the rate slows slightly, and again a pair of inverted complexes appears. The final complex is deformed somewhat by a movement of the string.

Lead IV (Fig. 3, *K*) shows a pair of alternating and a single premature ventricular contraction. The upwardly directed complex is quite similar to the one recorded upon admission (Fig. 1, *B*), the one preceding the paroxysm (*L*), and the upwardly directed complexes during the height of the paroxysm (Fig. 1, *C*). In *L* two upright complexes occur, after which the bidirectional tachycardia is established with gradually increasing rate. The inverted complexes are seen to change shape gradually during the first few beats. The termination of this paroxysm was not recorded.

Briefly, the following points may be made after study of the electrocardiograms:

1. The most often encountered premature ventricular systole was of the right ventricular type, originating below the bifurcation. This extrasystole was similar to the one originating the tachycardia, yet it was not identical to the complex present during the height of the paroxysm.

2. This premature beat appeared alone, or was followed either by an alternating complex (Fig. 3, *C* and *E*) or another aberrant (fusion?) form (Fig. 3, *I*).

3. The coupling time of this premature complex with the preceding supraventricular complex was variable, which makes a re-entry theory difficult to defend.

4. The longest coupling time was longer than the shortest distance between two supraventricular complexes. Thus, an aberrant pathway alone could not account for the shape of the extrasystole if it originated above the bifurcation.

5. In spite of the difficulty in measuring the prematurity of these contractions because of the underlying auricular fibrillation, the pause that followed these ectopic beats was longer than the usual distance between two supraventricular contractions, and appears "compensatory."

6. There was a striking regularity of the alternating complexes in the middle of the paroxysms; there was a definite irregularity at the onset and termination, consisting of irregularities of rate, alternation, and contour.

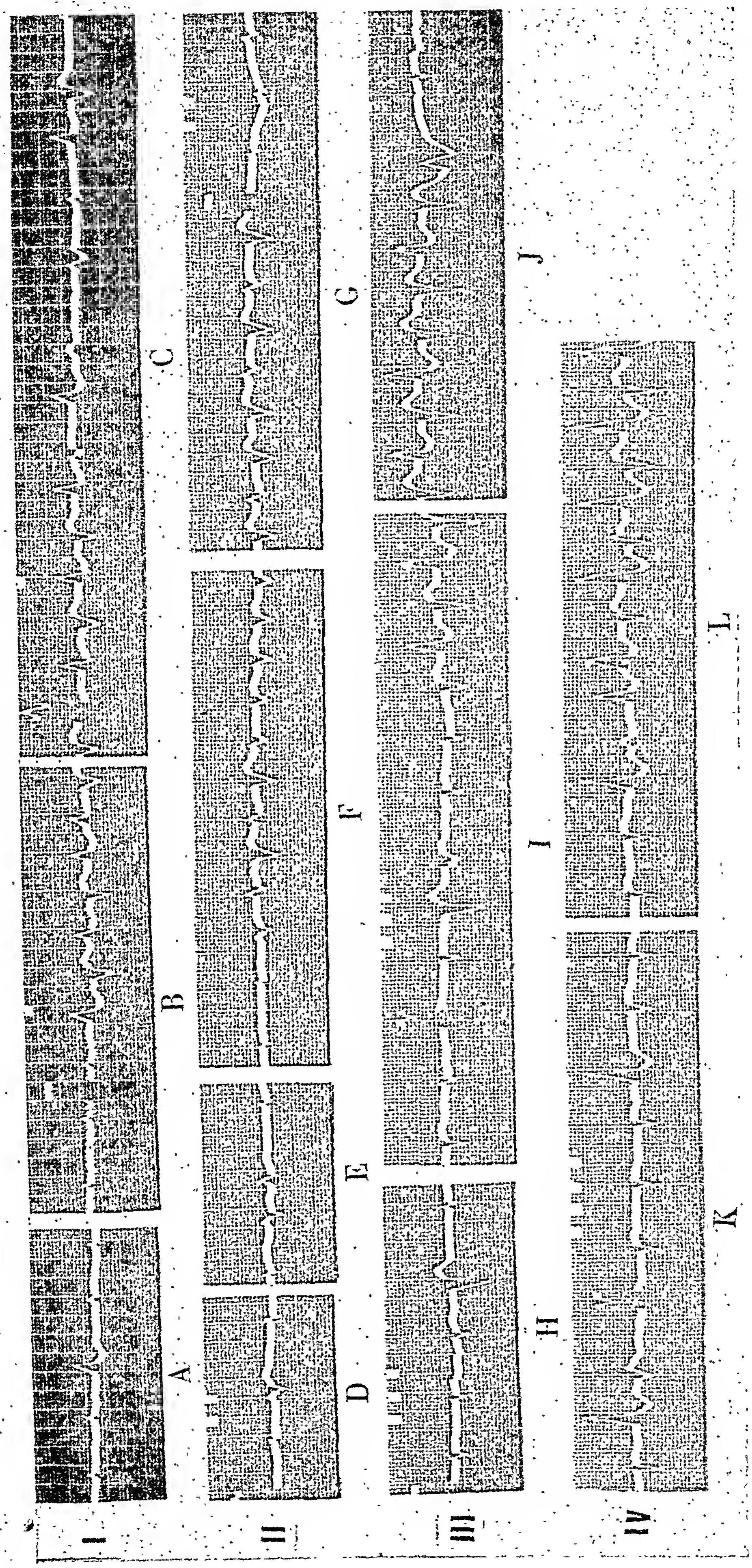


Fig. 3.—Shows the electrocardiographic pattern of sections between the paroxysms (*A*, *D*, *E*, *H*, and *K*), the onsets of paroxysms in four leads (*B*, *F*, *I*, and *L*), and endings in the extremity leads (*C*, *G*, and *J*).

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7. The ends of the paroxysms showed no definite pattern except a gradual slowing of the rate and a rather long "compensatory" pause before the supraventricular complexes reappeared.

8. Impairment of conduction might explain minor variations in the size and shape of the complexes, but it is hard to explain the regular alternation of complexes at the height of the paroxysm simply upon this basis. Impairment of conduction should be accompanied by more variations in the configuration of the complexes.[16]

9. A simple or modified figure-of-eight circus wave, besides lacking experimental evidence and an anatomic basis, should be extinguished by the premature beat in Fig. 3, *C*, yet the upward complex appeared again.

10. Measurements of the distance between cycles was very unreliable, even in parts of the curve that were technically perfect. Irregularities of rate could not be demonstrated by measurement during the height of the paroxysm.

11. In view of these observations, it would seem that numerous ectopic foci in the ventricular myocardium below the bifurcation produced the bidirectional ventricular tachycardia, either by a fusion phenomenon or by the domination, eventually, of two centers of similar rates during the height of the paroxysm.

SUMMARY

A case is reported in which a series of attacks of bidirectional ventricular tachycardia followed, upon two occasions, the use of *Digitalis purpurea*. Strophanthin and *Digitalis lanata* produced no such toxic effects.

Study of the electrocardiograms in this case does not substantiate the currently favored theories of the origin of this disturbance. The assumption that multiple ectopic foci are present in the damaged myocardium and are responsible for this alternating paroxysmal ventricular tachycardia cannot be avoided. The height of the paroxysm may be the result of interference phenomena, or of the predominance of two centers of the same order over the other ectopic foci, evidence for which may be seen at the beginnings and endings of the paroxysms. Such a theory has the advantage of explaining the different forms of paroxysmal tachycardia.

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Precordial trauma produces various electrocardiographic alterations and is not related to the localization or the intensity of the anatomic damage. Sometimes it is possible to find electrocardiographic alterations and no apparent anatomic damage which might be attributed to a phenomenon of cellular commotion.

The results of this experimental study demand further investigation in the cardiac aspects of our patient of precordial trauma. They also suggest a careful investigation into the traumatic background of some cardiac patients whose etiological factors remain unknown.

AUTHORS.

Moses, C., and Ferderber, M. B.: The Oscillometer and Thermocouple as Diagnostic Aids in Peripheral Vascular Disease. J. Lab. & Clin. Med. 29: 1147, 1944.

Observations relative to the peripheral circulation were made on one hundred two individuals. This group included forty-eight normal subjects, eight asymptomatic, six with thromboangiitis obliterans, and twenty-eight with arteriosclerosis. Observations as to history, symptoms, physical signs, oscillometric readings, skin temperatures, blood flow, and vibratory sensation were noted, and the results tabulated.

The techniques used in obtaining the data are briefly described.

While in arteriosclerosis of the lower extremity, symptoms referable to the calf were most common, pain was noted almost as frequently in the ankle, arch, dorsum, or toes. Numbness, tingling, burning, aching, and rest pain were symptoms noted almost as frequently as intermittent claudication in arteriosclerotic vascular disease. A feeling of local fatigue was often the first sign of vascular disease.

Arteriosclerotic rest pain was often relieved by moderate exercise. The pain of thromboangiitis obliterans was not relieved by exercise in any of our patients.

Normal distribution of the hair over the lower extremity was noted in only 25 per cent of the patients with vascular disease.

Rubor, cyanosis, or pallor of an extremity may be present in the absence of arterial vascular disease.

The absence of the dorsalis pedis or posterior tibial pulsation was not pathognomonic of vascular disease, and the presence of a pulsation did not exclude vascular pathology.

The oscillometric readings were not necessarily found to be decreased in arteriosclerotic peripheral vascular disease; normal individuals with heavy musculature may have diminished oscillometric readings.

Normal skin temperatures may obtain in individuals with vascular disease.

Estimation of the blood flow by Stewart's calorimetric method indicated that the blood flow in patients with vascular disease averaged about two-thirds of that in normal subjects.

Estimation of the vibratory sense by the method of Barach yields confirmatory evidence of deficient circulation but is of little early diagnostic value.

The arteriolovenous anastomoses are suggested as one mechanism partially explaining the variations in skin temperature that occur in normal individuals and those with peripheral vascular disease.

AUTHORS.

Paley, S. S., and Krell, S.: Fetal Electrocardiography and Stethography. Am. J. Obst. & Gynec. 48: 489, 1944.

An attempt was made to record fetal electrocardiograms and stethograms in twenty-one gravid women of varying periods of gestation. Positive fetal electrocardiograms were obtained in 53 per cent; positive stethograms were obtained in 79 per cent. Where large fetal electrocardiographic deflections were obtained they were diphasic, otherwise they were single downward spikes in all but one case. The latter was probably a breech presentation at the time the record was made.

Abstracts and Reviews

Selected Abstracts

Holt, J. P.: The Effect of Positive and Negative Intrathoracic Pressure on Cardiac Output and Venous Pressure in the Dog. Am. J. Physiol. 142: 594, 1944.

Cardiac output was measured by the direct Fick method and by a modification of Stewart's method in dogs breathing oxygen and air at pressures of 8 and 16 cm. of water below atmospheric, 8 and 16 cm. of water above atmospheric, and at atmospheric, pressure. The control cardiac output determinations made with the Fick method showed considerable variation, while the control determinations with the modified Stewart method showed little variation. The cardiac output determinations with the modified Stewart method showed that, when air under a positive pressure of 16 cm. of water was breathed, the cardiac output was decreased. The average decrease was 33 per cent of the control. When air under a negative pressure of 16 cm. was breathed there was little change in the cardiac output.

Peripheral venous and right auricular pressures were measured simultaneously in dogs breathing air from a chamber in which the pressure varied from 20 cm. of water pressure above, to 20 cm. below, atmospheric pressure. When air under a positive pressure of 16 cm. of water was breathed, the pressure fall from peripheral vein to right auricle was decreased. The average decrease was 72 per cent of the pressure fall when air under atmospheric pressure was breathed in one group of experiments and 64 per cent in another. When air under a negative pressure of 16 cm. of water was breathed, the pressure fall from peripheral vein to right auricle increased. The average increase was 191 per cent of the control pressure fall in one group of experiments and 244 per cent in another.

Since the cardiac output of the dog changes very little when air under a negative pressure of 16 cm. of water is breathed, it would appear that the maintenance of a high peripheral venous pressure, when right auricular pressure is greatly decreased, is due to the fact that the veins become partially collapsed just before entering the chest and increase the resistance to the flow of blood to the right auricle.

AUTHOR.

Forero, A., Silva, R., and Saffie, F.: Electrocardiographic and Anatomical Studies of Experimental Precordial Trauma. Rev. argent. de cardiol. 11: 77, 1944.

The authors studied the effect of precordial trauma on twenty-one cats. Many electrocardiographic curves were made in each one of them, before and after the trauma. Then the animal was killed and a macroscopic study of the whole heart and a microscopic study of the interventricular wall were made. The various factors which can influence the electrocardiographic curves and the anatomic alterations were studied. The final conclusions of this experiment were as follows:

Experimental precordial trauma on the cats produces electrocardiographic and anatomic alterations of the heart.

To a certain extent, the intensity of anatomic alterations is parallel to the violence of the blow. But many other factors play an important role, as elasticity of the thorax, cardiac and respiratory phase when the blow is applied, etc. As a consequence we can observe that equally intensive blows produce anatomic damage of different magnitude.

pare the information gained by such surveys as this with what is now known about rheumatic infections in military camps in the United States. There is a comparatively high incidence of rheumatic fever in the military forces in Colorado, Idaho, and Utah. These camps are in dry areas, removed from water courses, and at relatively high altitudes. Needless to say, poverty is no factor, and the housing, sanitation, and diet are excellent. In fact, there are only two features common both to the military forces in these states and to the impoverished civilians in areas with a high incidence of rheumatic fever, namely, (1) crowding and (2) inability to control the micro-climate. It is not always possible for either the poor man or the military man to rest whenever he is tired, get warm when he is cold, and keep dry when it is raining. In civilian life, poverty, diet, proximity to water courses, etc., might be said to be important only in so far as they are a part of the two features mentioned, and so reduce the power of the body to resist disease.

AUTHORS.

Paulley, J. W., and Aitken, G. J.: Case of Cardiovascular Beri-Beri. Lancet 2: 440, 1944.

A case of cardiovascular beriberi is described. Three etiological factors may be recognized: (a) marginal, and submarginal diet; (b) some alcohol, but not chronic alcoholism; and (c) possibly age. The patient presented the usual clinical features of cardiovascular beriberi, and showed a grossly deficient excretion of vitamin B_1. Circulation time (arm-lung) was abnormally long. Recovery was clinically complete in forty days.

AUTHORS.

Leiper, E. J. R.: Hypertension Associated With Unilateral Renal Lesion. Lancet 2: 439, 1944.

The question arises whether recovery was due to the removal of the diseased kidney, and what part, if any, was played by the right-sided sympathectomy. The evidence suggests, I think, that the role of the sympathectomy was insignificant, and that the benefit must be ascribed to the nephrectomy. Judging by the results of widespread bilateral removal of sympathetic ganglia and fibers (Jefferson, 1942; Takats et al., 1942), the dramatic cure here witnessed could scarcely have been the result of sympathectomy confined to one side. Nephrectomy, on the other hand, when successful, is usually strikingly so.

When a unilateral renal lesion is found in a patient with hypertension it does not by any means follow that the hypertension will disappear on removal of the kidney. The number of cures so far recorded is small.

AUTHOR.

Bigger, I. A.: Treatment of Traumatic Aneurysms and Arteriovenous Fistulas. Arch. Surg. 49: 170, 1944.

Twenty-nine cases of traumatic arterial aneurysm or arteriovenous fistula have been studied. Unfortunately, satisfactory follow-up studies have not been possible in a considerable number of cases but it is believed that evidence of some value has been obtained regarding the occurrence of subjective symptoms of chronic circulatory deficiency after obstruction of main arteries of the extremities. Eight of nine patients in whom one of the main arteries to the lower extremity was obstructed had follow-up examinations at periods of from nine months to eight years after operation. Seven of them have definite symptoms of chronic circulatory deficiency distal to the obstruction.

Excision of an aneurysmal sac is more certain to cure the lesion than aneurysmorrhaphy but has the disadvantage of destroying more collateral channels than does the intrasaccular operation. It is more reasonable to assume that interference with the

The weight of the mother and size of the fetus influence the successful demonstration of the fetal electrocardiogram, but the age of the mother, her parity, fetal presentation, and fetal sex are not factors in determining the production of fetal electrocardiographic deflections. The fetal cardiac rate bears no relationship to its sex; limb leads are of no value in obtaining fetal electrocardiograms; the best abdominal leads were those connecting the fundus of the uterus with the symphysis pubis; the pattern of a fetal stethogram resembles that of the adult; and the configuration of the sounds assumes the form of M, N, or W. The term embryocardia is a misconception.

AUTHORS.

Parkinson, D., Posch, J. L., and Stofer, B. E.: Tricuspid Mitral Valve: A Report of a Case, With a Suggestion as to the Mode of Development. Arch. Path. 38: 222, 1944.

A tricuspid mitral valve unassociated with any other congenital defects was observed in a 77-year-old farmer. The anterial lateral and medial cusps of this heart represent an incompletely fused anterial mitral cusp, and the posterior cusp, which is normally the smaller, represents the true posterior mitral leaflet.

AUTHORS.

Capaccio, G. D.: The Electrocardiogram After Exercise in Angina Pectoris. Northwest Med. 43: 144, 1944.

The electrocardiogram after exercise in angina pectoris is offered as an additional objective observation to confirm the clinical opinion. A negative (response to the exercise) test does not rule out the diagnosis of angina pectoris.

AUTHOR.

Feasby, W. R.: Rheumatic Fever in the Canadian Army. War Med. 6: 139, 1944.

About 4 per cent of persons with streptococcic disease of the respiratory tract acquire polyarthritis. The incidence of polyarthritis follows closely the incidence of streptococcic disease of the respiratory tract. Ninety per cent of the cases occurred in the first seven months of the year. Military populations most seriously affected were those of Saskatchewan and Alberta. No particular strain of streptococci accounts for these cases or their complications. The commonest type was A 19, which was predominant in the 1943 streptococcic epidemic at Camp Borden, Ontario.

From an analysis of four hundred seven such cases from the Canadian Army in Canada for 1943, it was found that (a) 24 per cent of the patients had cardiac complications, (b) 23 per cent are on full duty one year later, (c) 17 per cent are on low pulhems duty, and (d) 60 per cent are discharged and may be pensioned. The estimated cost for this group of cases is nearly $6,000,000 to be expended over the next thirty years. Approximately $700,000 has been spent to date for the 1943 cases. Preventive measures include proper dust control in sleeping quarters and adequate hospital isolation of persons with streptococcic illness.

AUTHOR.

Wedum, A. G., and Wedum, B. G.: Rheumatic Fever in Cincinnati in Relation to Rentals, Crowding, Density of Population, and Negroes. Am. J. Pub. Health 34: 1065, 1944.

This survey again emphasizes the importance of poverty and crowding in the genesis of rheumatic fever. However, poverty and crowding are only signposts pointing to a more fundamental epidemiological principle. It is instructive to com-

were killed at approximately twenty hours. The estimated maximum edema in these dogs was 20 to 47 ml. per kilogram of dog.

The above observations are not explainable on the basis of a reactive hyperemia in the traumatized legs alone. Accumulation of fluid in the legs is apparently an important factor in the induction of the shock state, but in many of the experiments the volume of edema appears to be insufficient of itself to explain the death. If the operation of humoral or nervous factors are not subsequently demonstrated to play a part in the induction of this type of shock we may have to revise downward our estimates of the quantity of local edema necessary to induce shock, especially in the absence of hemorrhage into the traumatized tissues.

The somewhat shorter survival and lesser edema in the second group of dogs demonstrates the importance of prolonged anesthesia and of restriction of activity in contributing to the ease with which shock with fatal outcome may be induced. Evidence is presented which suggests that dogs studied in the spring resist shock better than do dogs studied during the winter months.

AUTHORS.

Mazer, M., and Wilcox, B. B.: A Simple Graphic Method for Measuring the Area of the Orthodiagram. Am. J. Roentgenol. **51:** 444, 1944.

A simple graphic method for the determination of the area of the orthodiagram is described. It requires no equipment not readily available to any physician. Its application to one hundred cases checked by the planimeter shows it to have a sufficiently high degree of accuracy for clinical purposes.

AUTHORS.

Reynolds, J. T., and Jirka, F. J.: Embolic Occlusion of Major Arteries. Surgery **16:** 485, 1944.

Heparin should be administered as soon as the diagnosis of arterial embolus is made. This is done in order to prevent a thrombosis of the blood distal or central to the embolus, which, should it occur, would make all attempts to restore blood flow futile.

Sympathetic block should not be used in aortic, iliac, or femoral embolic occlusion until the operation has been done, because the resultant vasodilatation may allow the clot to progress and escape into vessels from which it can no longer be removed with ease.

Embolectomy should be done as soon as possible after diagnosis.

Most occlusions of the femoral and iliac arteries and the aorta may be satisfactorily displaced by approach through an incision in the femoral artery.

Emboli in popliteal and axillary vessels require removal only when the use of muscles supplied by the vessels remains impossible.

Heparin, intermittent venous compression, antispasmotics, and/or sympathetic blocks should be used as forms of treatment accessory to embolectomy. They should also be used when no embolectomy is done. Their use must be continued for some time.

Attention must be constantly directed to the cardiac disease which in itself may be fatal.

Twenty-four patients with twenty-seven limbs rendered ischemic by embolic occlulusion have been studied. Of these limbs, nine were not operated upon. Eighteen limbs were operated upon. In one patient the embolus had moved, and in a second the embolus could not be obtained. Thus, there were sixteen limbs from which an embolus was removed at operation from thirteen patients.

Ten of these emboli were removed within eight hours of their occurrence; all of the patients had satisfactory return of the circulation. Of the remaining six

collateral arteries would increase the danger of ischemic gangrene and would also increase the degree of chronic circulatory deficiency.

An atypical or incomplete operation may result in cure of a traumatic aneurysm, but an arteriovenous fistula is rarely cured except by complete ligation of the involved vessels and excision of the fistulous area or by suture of the artery. If the latter procedure is employed it is usually better to ligate the vein above and below the fistula and then to open the vein and suture the artery under direct vision.

Evidence is also presented which indicates that while the excellent collateral circulation developed in the presence of an arteriovenous fistula makes the danger of ischemic gangrene almost negligible, it does not prevent persistent circulatory difficulty when main vessels are ligated and resected. It is therefore suggested that, when such important vessels as the carotid artery and jugular vein, the common femoral vessels, or the popliteal vessels are the site of arteriovenous fistula, transvenous repair of the artery be employed if there are no contraindications. The most important contraindication to arterial suture is calcification of the wall of the artery in the area to be sutured.

When the main vessels are obstructed, especially those to the lower extremity, permanent interruption of the sympathetic nerves to that extremity may help prevent chronic circulatory deficiency distal to the obstruction.

AUTHOR.

Green, H. D., Dworkin, R. M., Antos, R. J., and Bergeron, G. A.: Ischemic Compression Shock, With an Analysis of Local Fluid Loss. Am. J. Physiol. **142:** 494, 1944.

An ischemic trauma was produced by application of rubber tubes in the form of a tight continuous spiral bandage from the ankle to the groin of both hind legs of dogs anesthetized with morphine and sodium pentobarbital. Upon release of the tubes after 6 or more hours compression, death occurred in twenty-four of a first group of twenty-five minimally anesthetized dogs which were free to move about in their cages, and in all of a second group of fourteen dogs anesthetized for longer intervals and restricted to animal boards in a supine position. The dogs of the first group survived 0.8 to 50 hours after release of the rubber tubes, with an average survival of 11.8 hours. The dogs of the second group survived 2 to 20 hours with an average survival of 7.9 hours.

Following the release of the rubber tubes the mean arterial pressure in the dogs of the second group fell rapidly from around 170 to 180 mm. Hg to around 120 to 150 mm. Hg accompanied by a marked rise in heart rate, and a reduction of blood flow in the forepaws, as indicated by subcutaneous temperature records. The mean arterial pressure then declined more slowly to about 50 to 60 mm. Hg, after which death from respiratory or cardiovascular failure ensued within a relatively few minutes. Collapse of the peripheral veins was noted during the period of declining arterial pressure. The hematocrit reading rose rapidly during the first hour after removal of the rubber tubes and continued to rise slightly during the ensuing hours. Depression of activity and sluggish response to stimulation were seen in the lightly anesthetized dogs after release of the limb compression.

The accumulation of fluid in the traumatized extremities was measured by immersion of the legs separately in a suitable tall narrow vessel before applying the rubber tubes and again after death. After allowing 5 ml. per kilogram of dog per extremity for shrinkage of the legs with death, and after allowing for the fact that immersion may measure only 91 per cent of the true edema, the estimated maximum volume of edema still ranged from 15 to 56, with an average of 41.3 ml. per kilogram of body weight in the dogs of the first group and from 3.3 to 33 with an average of 17.6 ml. per kilogram of body weight in the second group of experiments. One leg only was traumatized in seven dogs. Three of these died with an estimated maximum volume of edema of 33, 33, and 55 ml. per kilogram. The remaining four

then completely disappeared, and the patient has remained entirely well to date, one and one-half years after surgery. The cellophane was thought to be responsible for the final complete and permanent occlusion of the patent ductus arteriosus.

AUTHORS.

Wakerlin, G. E., Johnson, C. A., Moss, W. G., and Goldberg, M. L.: Treatment of Experimental Renal Hypertension With Renal Extracts. J. Pharmacol. & Exper. Therap. 81: 101, 1944.

The antihypertensive effect of partially purified hog renin in renal hypertensive dogs is definitely superior to highly purified hog renin, suggesting that the active principle is in the nonrenin fraction.

Partially purified heat-inactivated hog renin possesses moderate antihypertensive activity, indicating that the active principle is partially heat-stable.

Partially purified dog renin is not antihypertensive in three times the effective dose of hog kidney, suggesting either that the concentration of the antihypertensive principle is considerably less in dog kidney or that some type of immune response not evoked by homologous renal extract is involved.

Hog liver extract prepared after the manner of partially purified renin was ineffective antihypertensively, suggesting that the antihypertensive potency of our hog renal extracts is not due to a foreign protein effect and that the potency is specific for kidney.

A role for antirenin in the antihypertensive mechanism is largely excluded.

A study of the antihypertensive potency of the nonrenin fraction of partially purified hog renal extract containing renin is well warranted and now under way.

AUTHORS.

Jacobs, J., and Yonkman, F. F.: Sympatholytic Treatment of Experimental Hypertension. J. Lab. & Clin. Med. 29: 1217, 1944.

Yohimbine hydrochloride, 20 mg. per kilogram of body weight when orally administered, reduces the mean arterial tension of dogs rendered hypertensive by the Page technique of perirenal envelopment.

Reduction of arterial tension was effected in three of four dogs. One was of real significance, another of some, and the third was inconsequential; these appraisals were made after thirty-five, thirty-three, and twenty-three days of medication, respectively. Sustained medication for longer periods would be desirable.

The locus of yohimbine's pharmacologic action in this type of hypertension is probably in the neuromuscular receptors associated with sympathetic vasoconstrictors and is probably antiadrenergic or sympatholytic in nature.

AUTHORS.

Thomas, C. B., and McLean, R. L.: The Effect of Intravenous Injection of Epinephrin and Angiotonin Before and After the Production of Neurogenic Hypertension. Bull. Johns Hopkins Hosp. 75: 319, 1944.

The pressor responses of unanesthetized dogs to epinephrine and angiotonin were not significantly altered by the induction of neurogenic hypertension.

Angiotonin produces a well-marked cardiac acceleration in the hypertensive animal, whereas it slows the cardiac rate slightly when the dog is in the normal state. Epinephrine has a similar but less marked effect upon the heart rate.

These experiments indicate that while peripheral vasoconstrictor activity may be increased in neurogenic hypertension, vasoconstrictor tone is not sufficiently great to interfere with the action of either sympathicomimetic or humoral vasoconstrictor substances.

It appears that angiotonin stimulates the cardio-accelerator mechanism, but that this effect is normally masked by the moderator reflexes.

AUTHORS.

patients, four were successfully treated (one after twenty-seven hours), one result was doubtful, and one was a failure.

Twelve of the patients studied died. All of these had had emboli removed. Seven patients died within the first few days after the removal of the embolus, apparently from cardiac failure, and all had had successful restoration of the peripheral circulation. Death in four of the remaining five was from causes not related to the heart disease or the embolus and might therefore have been avoided.

AUTHORS.

Barber, R. F., and Madden, J. L.: **Resuscitation of the Heart.** Am. J. Surg. 64: 151, 1944.

Acute stoppage of the heart is a surgical emergency demanding immediate action if complete recovery is to be obtained. A preconceived plan of therapy avoids delay and confusion.

The percentage of complete recovery in resuscitation of the heart will vary in direct ratio to the time interval between cardiac stoppage and the production of an adequate circulation by massage.

The maintenance of a free and adequate artificial respiratory exchange during the course of resuscitation of the heart is essential.

The cases of cardiac stoppage, capable of complete resuscitation, are those resulting from asphyxia, reflex vagal inhibition, cardiac trauma, cardiac toxins (drugs, anesthetics), acute cardiac dilatation, hemorrhage and vasomotor paralysis with resulting circulatory insufficiency, and electrocution.

The indiscriminate use of the intracardiac injection of epinephrine or other sympathomimetic drugs is condemned.

Sympathomimetic drugs should not be administered during the course of cyclopropane anesthesia.

Procaine hydrochloride (2 per cent) administered prior to, or simultaneous with, the intracardiac injection of epinephrine lessens the possibility of ventricular fibrillation occurring.

The topical application of procaine (5 per cent), metycaine (10 per cent), or cocaine (4 per cent) may also be used to the surface of the heart; the injection of the 2 per cent solution into the chambers of the heart and electrical countershock are the most efficient methods in the treatment of ventricular fibrillation.

The transthoracic approach is the method of choice in the performance of cardiac massage. Exposure of the heart is obtained through a transverse incision in the left third or fourth interspace, the adjacent costal cartilages sectioned, and the corresponding ribs widely retracted.

Manual massage of the heart is the most effective means of initiating cardiac contractions. If uniform success is to be obtained, massage must be performed within three minutes following cessation of the heart beat.

AUTHORS.

Harper, F. R., and Robinson, M. E.: **Occlusion of Infected Patent Ductus Arteriosus With Cellophane.** Am. J. Surg. 64: 294, 1944.

A case of patent ductus arteriosus in an adult woman, complicated by long standing, severe, subacute, bacterial endocarditis and endarteritis is reported. The patent ductus arteriosus was occluded by ligating it with two silk ligatures and then wrapping cellophane loosely about it. The clinical postoperative course of the patient demonstrated the fact that the cellophane was responsible for the final complete occlusion of the patent ductus arteriosus. For the first two weeks the murmur and symptoms disappeared only to reappear and persist until two and one-half months had elapsed from the time of operation. The murmur and symptoms

American Heart Association, Inc.

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**Executive Committee.*

Book Reviews

ELEMENTS OF ELECTROCARDIOGRAPHIC INTERPRETATION: By Louis N. Katz, M.D., Director of Cardiovascular Research, Michael Reese Hospital, Chicago, and Victor Johnson, Ph.D., M.D., both Professorial Lecturers in Physiology, University of Chicago. University of Chicago Press, Chicago, 1944, ed. 3, 44 pages, 40 illustrations, $1.00.

The purpose of the authors, to provide a booklet "suitable for use by the physician whose specialty lies outside the field of electrocardiography and by the beginning student of cardiac physiology," should be well achieved by this publication. The introductory statements are brief but adequate for a booklet of this character, the plates illustrating electrocardiograms are logically arranged, and the tracings are well reproduced.

The reviewer, however, doubts the wisdom of including, in a work of this type, records whose interpretation is open to any question. The electrocardiogram shown in Plate 9 is certainly one of doubtful character, and, unless students in Chicago are brighter than those elsewhere, one wonders how much this tracing helps to clarify cardiac physiology. Plate 7 should also cause trouble. This electrocardiogram is reproduced as an example of A-V nodal rhythm because of an unusually short P-R interval. The P waves are, however, not inverted, but definitely upright in Leads II and III, which makes it clear that the auricles were not activated from a rhythm center in the A-V node. The record is probably, in the opinion of the reviewer, an example of the so-called Wolff-Parkinson-White syndrome.

Only one definite error was found in the booklet. This occurs in Plate 36, in the first group of tracings. Leads I and II are interchanged, and the latter (Lead I in the figure) is upside down.

The material given in Appendix II, relative to recommended procedure in reading an electrocardiogram, should help those not familiar with interpretation of tracings to approach the records in a logical and systematic fashion.

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explains the syndrome in its entirety. The most promising and most widely accepted view was put forward independently by Holzmann and Scherf[6] and by Wolferth and Wood.[7] They suggested that the short P-R interval and the broad QRS complex are due to the transmission of impulses from auricles to ventricles by way of an accessory atrioventricular bundle, a strand of muscle of the sort described originally by Kent.[8] Quite recently, this conception has been supported by two important studies. In experiments on animals, Butterworth and Poindexter[9] passed action currents picked up from the auricular surface through a vacuum-tube amplifier and utilized the output to excite the ventricles. In this way they were able to obtain electrocardiograms strikingly similar to those seen in human cases of anomalous atrioventricular excitation. By reversing the connections and applying amplified ventricular action currents to the auricles they were also able to induce paroxysms of tachycardia simulating those often observed in this syndrome. Wood, Wolferth, and Geckeler[10] have reported a careful histologic search for muscular bridges between the auricular and the ventricular myocardium in a case of anomalous atrioventricular excitation in which death occurred during an attack of paroxysmal tachycardia. Three connections of this kind were found on the right side of the heart.

These studies are of very great importance, but they must be regarded as suggestive rather than decisive. The experiments of Butterworth and Poindexter[9] demonstrated that excitation of the epicardial surface of the ventricles by the action currents of adjacent auricular muscle, or inferentially by the transmission of auricular impulses across an accessory atrioventricular bundle, could account for the brevity of the P-R and the abnormal length of the QRS interval, and also suggested a way in which a physiologic or anatomic anomaly of this sort might lead to paroxysms of tachycardia. Nevertheless, they left many questions relating to these phenomena unanswered. Muscular bridges of the kind found by Wood and his co-workers[10] were originally described by Kent,[8] and have recently been observed by Glomset and Glomset[11] in hearts that were presumably normal. It would appear, therefore, that human hearts in which they can be found are much more numerous than those that exhibit anomalous atrioventricular excitation. This consideration raises doubt as to their significance.

In view of this situation, it seemed desirable to ascertain whether unipolar precordial and esophageal leads, which have proved of great value in the study of other abnormalities of the ventricular complex, would yield data consistent with the hypothesis in question.

CLINICAL OBSERVATIONS

We have had the opportunity of studying ten cases of anomalous atrioventricular excitation which were discovered in the course of routine electrocardiographic examination or referred to us for investigation.

American Heart Journal

Vol. 29 March, 1945 No. 3

Original Communications

THE POTENTIAL VARIATIONS OF THE THORAX AND THE ESOPHAGUS IN ANOMALOUS ATRIOVENTRICULAR EXCITATION (WOLFF-PARKINSON-WHITE SYNDROME)

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INTRODUCTION

In 1930, Wolff, Parkinson, and White[1] reported a group of cases characterized by the following features: (1) the occurrence of paroxysms of tachycardia, heterotopic in origin; (2) complete absence of physical signs of heart disease when the heart rate was normal; (3) electrocardiographic peculiarities, of which the most striking were abnormal shortening of the P-R interval and a pronounced increase in the duration of the QRS complex; (4) reversion of the anomalous electrocardiogram to the normal form either spontaneously, after exertion, or after the administration of atropine. Isolated cases which seem to have been of a similar kind had previously been reported by Wilson,[2] Wedd,[3] and Hamburger.[4] In 1940, Hunter, Papp, and Parkinson[5] were able to find ninety cases of this type in the literature and to add to these nineteen cases which they had collected. This condition has been called the Wolff-Parkinson-White syndrome, but in order to avoid awkward forms of expression we shall more often refer to it as anomalous atrioventricular excitation.

A number of different hypotheses have been advanced to account for the peculiarities of cardiac mechanism which make this disorder unique. These hypotheses have recently been reviewed and classified by Hunter and his associates, and it is fair to say that none of them satisfactorily

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Much of the work upon which this article is based was done under a grant from the Horace H. Rackham School of Graduate Studies.

Presented in part before the Sixteenth Annual Meeting of the Central Society for Clinical Research, Chicago, Nov. 5, 1943.

Received for publication May 9, 1944.

CASE 5.—A young man, aged 34 years, was referred to the William J. Seymour Hospital (Eloise, Mich.) on July 30, 1941, for examination in connection with the Selective Service program. He presented no cardiac symptoms. The blood pressure was 190/120, and there were mild changes in the retinal arteries of the kind often associated with arterial hypertension. The heart was not definitely enlarged either on physical or roentgenographic examination. The remainder of the physical examination was negative.

CASE 6.—A male physician, aged 28 years, who was attached to the Heart Station, was found to have an anomalous tracing when he was used as a subject in the course of a test of some electrocardiographic equipment. He was subject to renal glycosuria, but was otherwise well, and physical and roentgenographic examination of the heart was negative.

CASE 7.—A male laborer, 37 years old, entered the hospital June 9, 1934, complaining primarily of joint pains associated with swelling and limitation of motion. For about three years he had also been subject to paroxysms of tachycardia lasting from twelve to twenty-four hours. These were accompanied by mild dyspnea, slight precordial distress, and occasional choking sensations. The heart was not enlarged, but roentgenographic examination disclosed slight widening and tortuosity of the thoracic aorta and minor prominence of the pulmonary artery. Frequent extrasystoles were noted, but no murmurs were heard, and the blood pressure was normal. The knees, elbows, and wrists showed changes characteristic of chronic atrophic arthritis, and there was some hypertrophic arthritis of the spine. The patient was under treatment for a considerable period, during which a number of paroxysms of tachycardia, supraventricular in origin, were observed. These were successfully treated with acetyl-β-methylcholine chloride and with quinidine. The regular administration of the latter reduced the frequency of the attacks.

CASE 8.—A female clerk, aged 24 years, requested an examination on July 29, 1943. She had been rejected for service with the Armed Forces on account of a cardiac murmur and arrhythmia. Examination disclosed a fairly loud, late systolic, apical murmur and an inconstant systolic click. Sinus arrhythmia and occasional extrasystoles were noted. The blood pressure was normal, and the remainder of the physical examination was negative.

CASE 9.—A male office worker, 25 years old, was examined Oct. 6, 1941, with reference to frequent attacks of rapid heart action during the preceding ten years. One of the most recent of these had persisted for thirty hours. Physical examination of the heart was negative, and the blood pressure was normal. Roentgenographic examination of the chest and the routine laboratory tests gave no further information.

CASE 10.—A housewife, aged 48 years, was admitted to the William J. Seymour Hospital (Eloise, Mich.) because of an involutionary psychosis early in February, 1941. She gave a history of paroxysms of tachycardia, but had no other symptoms referable to the heart. No cardiac abnormalities were discovered on examination, and the blood pressure was normal. This patient is still under observation; her mental condition has gradually deteriorated.

In summarizing the clinical aspects of these ten cases of anomalous atrioventricular excitation we may mention that all of the patients were under 50 years of age, and that all except two were males. Three ex-

Brief abstracts of the case histories are presented below. The electrocardiographic data will be considered separately.

CASE 1.—A schoolboy, aged 13 years and of somewhat deficient intelligence, entered the hospital Oct. 7, 1942, for the correction of convergent strabismus which had been present since infancy. Along the left margin of the sternum there was a moderately loud, rough, systolic murmur, but the heart was not enlarged; the blood pressure was normal, and there were no cardiac symptoms. A corrective operation on the eyes was performed October 29, and the patient's convalescence was uneventful.

CASE 2.—A male professor, aged 36 years, came in for a checkup examination on Feb. 14, 1942. He had no complaints referable to the heart and appeared to be in good health. Soft systolic murmurs were heard at the cardiac base and apex, but there was no enlargement of the heart either on physical or roentgenologic examination. Apart from the anomalous electrocardiogram, no abnormalities of any sort were discovered. Late in July, 1942, this man was found dead in his automobile, which was standing at the side of the road. He was known to have been normally active a few days prior to his death. The results of an autopsy carried out by the coroner could not be ascertained.

CASE 3.—A male storekeeper, 34 years of age, entered the hospital March 20, 1942, complaining of occipital headaches for the preceding four years, and of mild dyspnea on exertion and slight edema of the ankles for several months. During the preceding three years he had been subject to paroxysms of tachycardia, forty-five minutes to four hours in duration. The blood pressure was 186/116; there was slight edema of the ankles, and the heart was slightly enlarged to the left. The urine contained albumin and granular casts, and renal function was depressed (urea clearance, 29 and 22 per cent of normal). There was no improvement on a conservative regime, and a bilateral splanchnicectomy was performed Aug. 31, 1942. Twelve days later the patient was discharged; at this time the blood pressure was 105/55. He returned for a checkup examination on Aug. 16, 1943, and reported that he had had a few attacks of tachycardia, but was working regularly. The blood pressure was then 162/120; apart from the absence of edema, the physical signs were not notably different from those found on previous occasions. There was, however, a change in the electrocardiogram; the T deflections, previously inverted in precordial leads V_4, V_5, and V_6, had become upright. It has been observed that the inverted T waves often seen in hypertensive heart disease frequently return to normal after operations of the kind performed on this patient.

CASE 4.—A foundry worker, 30 years old, entered the hospital Nov. 11, 1942, complaining of attacks of nocturnal dyspnea and palpitation. Three attacks of this sort had occurred during the preceding three months. The duration of the paroxysms varied from ten to fourteen hours, and attempts to prevent them by the administration of digitalis and quinidine had not been successful. There was a moderately loud, apical, systolic murmur, but the heart was not enlarged either on physical or roentgenographic examination, and the blood pressure was normal. The rest of the physical examination and the routine laboratory tests were negative. The administration of quinidine, 0.2 Gm. three times daily, was advised, but this treatment failed to prevent occasional paroxysms of tachycardia.

bundle and spreads through the ventricular walls from within outwards. The various types of QRS complexes inscribed in unipolar precordial leads under these circumstances may be interpreted with confidence because the principles involved have been established by recording and comparing the potential variations of the epicardial surface, the ventricular cavities, and the precordium in experiments on animals. We cannot, however, assume that a QRS pattern which has a known significance when ventricular excitation takes place in the normal fashion must have the same significance when auricular impulses are transmitted to the ventricles along anomalous paths.

Previous observers have found that when anomalous and normal beats are recorded in the same tracing, the sum of the P-R and the QRS interval is the same, or very nearly the same, for both. This suggests that the broad QRS complexes represent premature anomalous activation of the ventricular muscle, combined with normal activation by way of the His bundle. Assuming that this is true, we must conclude that, in relation to auricular events, some fraction of this muscle is activated earlier, but none can be activated later, than would be the case if the cardiac impulse reached the ventricles by way of the His bundle only. We may, then, refer to that part of the anomalous QRS complex which encroaches upon the normal P-R interval as the premature component. The point at which this component ends cannot be ascertained with certainty unless normal ventricular complexes have been recorded on the same tracing. In other cases we may consider that this point falls about 0.08 to 0.10 second ahead of the RS-T junction. We may also speak of the anomalous QRS complex as consisting of an anomalous component and a normal component. The former, which represents action currents produced by muscle activated by way of an aberrant pathway, is in part premature and in part superimposed upon the latter, which represents the action currents of muscle activated by the normal route. It has been observed that the premature component, that is to say, the premature part of the anomalous component, is almost invariably of relatively low voltage and displays no steep slopes. In the majority of cases it is fused with the first part of the succeeding fraction of the QRS complex, and gives rise to basal slurring or notching of the earliest prominent QRS deflection. The size and character of this premature component have been interpreted as evidence that when the aberrant impulse first reaches the ventricular muscle it spreads slowly and does not immediately gain access to the Purkinje plexus. One of the principal objects of our investigation was to ascertain, if possible, the location of the muscle activated prematurely by an anomalous route.

The Type Case of Group A.—Depending on the form of the ventricular complex in precordial leads, we have divided our cases into two groups, A and B. Case 1 is the type case of the first group. In this instance, reversion of the anomalous to the normal type of electrocardiogram sometimes occurred spontaneously and could be induced by the ad-

hibited anomalies other than that involving the heart; we refer to the presence of renal glycosuria in Case 6, of mental deficiency and strabismus in Case 1, and of an involutional psychosis in Case 10. Half of the patients were subject to paroxysms of rapid heart action. Clinical evidence of structural heart disease was found in only one instance, in which it was associated with arterial hypertension. One other patient had an abnormally high blood pressure (Case 5), one had chronic atrophic arthritis (Case 7), and a third died suddenly and unexpectedly from an unknown cause (Case 2).

ELECTROCARDIOGRAPHIC OBSERVATIONS

Material.—The standard limb leads and unipolar* precordial leads from the six standard precordial points (Leads V_1 to V_6, inclusive) were taken in all ten of the cases upon which this report is based. Unipolar leads from the tip of the ensiform process (V_E) were taken in eight cases, multiple unipolar leads from the back and right side of the chest in five, and multiple unipolar leads from the esophagus in four. The esophageal leads were taken in the manner described by Nyboer,[12] and the unipolar limb leads according to Goldberger's technique.[13]

The analysis of our records would have been easier if we had taken all of the leads mentioned in every instance. Sometimes we did not do this because the time and length of the patient's visit did not offer the opportunity. More often, however, a number of these leads were not taken because the problems which prompted us to employ them at a later stage of our work had not yet presented themselves.

The Working Hypothesis and Its Implications.—We accepted, as a working hypothesis, the view that in cases of the kind under consideration auricular impulses reach the ventricles by way of an accessory atrioventricular bundle. If this is the case, it is clear that the order of ventricular activation during the first part of the QRS interval must depend to a considerable extent upon whether the ventricular muscle in which this bundle terminates lies on the inner or on the outer aspect of the ventricular wall. It must also be acknowledged that, if the existence of one anomalous tract of this kind is admitted, we cannot dismiss the possibility that two or more may exist. There are, moreover, reasons for supposing that, even if other atrioventricular bridges are present, the His bundle continues to function.

These considerations make the interpretation of the ventricular deflections which depict anomalous atrioventricular excitation particularly difficult. The situation is much more complicated than those encountered in the analysis of the curves that represent bundle branch block, ventricular hypertrophy, and myocardial infarction. In these conditions the cardiac impulse reaches the ventricles by way of the His

*The term *unipolar* is used to indicate that the exploring electrode was paired with a *central terminal* connected through resistors of 5,000 ohms to each of the extremity electrodes employed in taking standard limb leads. For practical purposes it may be assumed that the potential of a central terminal of this sort is *not affected* by the heart beat; or what amounts to the same thing, that it is zero throughout the cardiac cycle.

limb. The S component of the anomalous and that of the normal QRS complex are largest in the same lead (V_2). The former is small in the leads from the left side of the precordium and the lead from the ensiform process. In Lead V_1 a broad, bifid R wave is the only QRS component. The Q deflection of the normal complex of Lead V_5 does not occur in its anomalous companion. The differences between the T waves of the two kinds of ventricular complexes are as great as the differences between the QRS deflections. The long Q-T interval in Lead V_1 seems to be due to the fusion of a large U wave with the terminal part of T.

In the lead from the auricular level of the esophagus (Lead E_{29}), the difference in length between the P-R interval of the anomalous and that of the normal beats is especially conspicuous. The auricular and ventricular complexes of the latter are of the kind usually seen in unipolar leads from this region. The anomalous complexes are similar in general outline, but the QRS interval is much longer, the descending limb of QS has a much more gradual slope, and the T wave is upright. In the esophageal lead from a point 6 cm. farther from the nares (Lead E_{35}), the initial, slurred part of the QRS complex is still below the isoelectric line, whereas, in the leads from still lower levels (Leads E_{41} and E_{51}), this premature component is positive. The normal ventricular complexes of these last leads are very similar to, and the anomalous complexes very different from, those of the same species in Lead V_5. The deflections of Lead E_{51} are like those of Lead E_{41}, except that the anomalous beat displays a conspicuous R′ which follows the onset of P by approximately the same interval as the R summit of the normal beat. When the long axis of the heart occupies a relatively vertical position, leads from these levels of the esophagus (12 cm. or more below the level

TABLE I

CASE 1. INTERVALS IN FIG. 2. MEASUREMENTS IN SECONDS

LEAD	1		2		3		4	
	a	n	a	n	a	n	a	n
V_1	.093	.124	*{.138 .171	.139	-	.161	.191	.199
V_2	.101	.142	.166	.166	.188	.186	.220	.225
V_3	.096	.145	.172	.171	.202	.196	.220	.196
V_5	.085	.110	.153	.149	.175	.170	.195	.196
V_E	.097	.147	.181	.182	.203	.198	.225	.220
D_{III}	.068	.132	-	.173	.152	.153	.209	.199
E_{29}	.059	.128	-	.191	.154	.159	.190	.191
E_{35}	.071	.121	-	.166	.142	.142	.201	.183
E_{41}	.105	.135	.131	.174	.154	†{.147 .198	.207	.198
E_{51}	.117	.135	*{.139 .180	.175	‡{.162 .202	†{.147 .202	.220	.214

Key:
a—anomalous; n—normal.
Column 1—interval from beginning of P to beginning of QRS.
Column 2—interval from beginning of P to peak of R.
Column 3—interval from beginning of P to peak of Q, QS, or S.
Column 4—interval from beginning of P to end of QRS.
*Two R peaks present.
†First measurement to peak of Q, second to peak of S.
‡Two S peaks present.

ministration of amyl nitrite. Transitions from excitation of the one sort to excitation of the other were recorded in a variety of leads. In the standard limb leads the normal beats (labeled *n*) are represented by deflections of the kind often seen in the electrocardiograms of healthy young subjects (Fig. 1). In Lead I the QRS complex displays relatively small R and S components, and in Leads II and III it consists of a small Q wave followed by a tall R wave. The mean electrical axis of this complex has a nearly vertical direction, suggesting that the angle made by the long axis of the heart with the long axis of the trunk was a small one. The T waves are inverted in Lead III, as is often the case in electrocardiograms of this type. The anomalous beats (labeled *a*) are represented by patterns of very different form. Apart from the brevity of the P-R and the broadening of the QRS interval, there is conspicuous basal slurring of the first QRS component, and the mean electrical axis of QRS is nearly horizontal. The T deflections are inverted in Lead I. Normal complexes were recorded in only one of the unipolar limb leads, Lead V_F; in this lead they have the same outline as in Leads II and III. The anomalous complexes of Lead V_R show pronounced slurring of the first part of the large initial Q wave, and in Lead V_L the initial R deflection is deformed in a similar way.

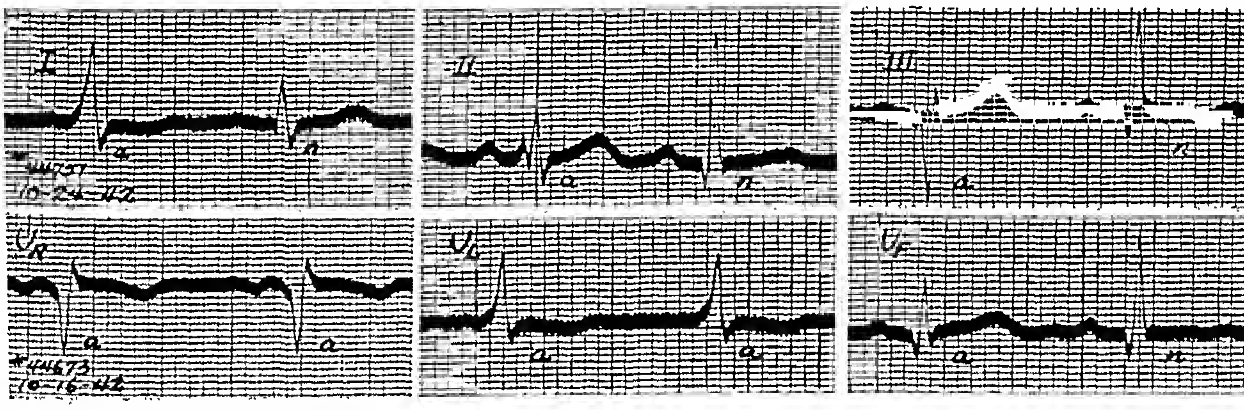

Fig. 1.—Case 1. Standard and unipolar limb leads. Complexes which represent anomalous atrioventricular conduction are labeled *a*, and complexes of the normal type are labeled *n*.

In Fig. 2, five unipolar precordial leads, a unipolar lead from a point overlying the spinal process of the eighth dorsal vertebra (D_{VIII}), and unipolar leads from four levels of the esophagus are reproduced. In the precordial leads the normal beats (labeled *n*) are represented by deflections of the usual type. In Leads V_1 and V_2 the R deflection is small, the R peak falls early in the QRS interval, and S is large; in Lead V_5 the R deflection is large, the summit of this deflection comes later, and small Q and S waves are present. In Leads V_3 and V_E the R and S deflections are approximately equal in size; we may speak of these leads as from the transitional zone. In all of these precordial leads the QRS complex of the anomalous beats (labeled *a*) is dominated by an R deflection which is considerably taller than the R wave of the normal beats and displays pronounced slurring of the basal part of its ascending

QRS component, (2) the peak of R, (3) the peak of the chief downward deflection (Q, QS, or S), and (4) the RS-T junction.

This table indicates that the anomalous P-R interval is certainly more than 0.02, and probably more than 0.05, second shorter than the normal P-R interval in this case. The largest difference was found in the lead from the auricular level of the esophagus, where it amounted to nearly 0.07 second. In Leads V_2, V_3, V_5, and V_E the R peaks of the paired complexes occur at the same time, within a few thousandths of a second, in relation to auricular events. In Lead V_1 the first peak (0.138) of the bifid R of the anomalous complex corresponds to the R summit (0.139) of the normal complex. In Lead E_{11} the R peaks of the two kinds of complexes do not correspond (0.131 and 0.174), and evidently differ in origin. In Lead E_{31} the normal R deflection corresponds in time not to the initial R, but to R′ of the anomalous complex. The paired intervals of the third column of Table I, which give the times of the apices of the largest negative QRS deflections, are in good agreement. In the case of Lead E_{41}, the apex of the anomalous S (0.154) corresponds more nearly to the apex of the normal Q (0.147) than to that of the normal S (0.198). The paired intervals of the last column, which give the time of the RS-T junction in relation to the beginning of P, are also alike except in two or three instances (Leads D_{VIII}, E_{35}, and E_{41}), in which the end of one or both of the QRS complexes is poorly defined.

These measurements clearly support the view that the excitatory process reached the epicardial surface of the anterior wall of the left ventricle at the normal time (in relation to auricular events) and by the normal route, even when some parts of the ventricular myocardium were activated prematurely by an anomalous mechanism. We cannot regard it as fortuitous that the R peak of the anomalous and that of the normal QRS complex of the leads from the left side of the precordium are separated from the beginning of the P wave by the same interval. It is clear, then, that the premature component of the anomalous QRS complex of these leads cannot be ascribed to forces produced by premature excitation of the anterior wall of the left ventricle. As regards the significance of this component in the leads from the right side of the precordium, the situation is similar. There is no evidence that the anterior wall of the right ventricle was activated prematurely. In Leads V_2 and V_E the single R peak of the anomalous, and that of the normal, beat bear the same relation to the P wave. This is likewise true of the first R summit of the anomalous, and the R peak of the normal, QRS complex in Lead V_1. The second R summit of this lead, which is somewhat like that seen in right bundle branch block, cannot be attributed to activation of the anterior wall of the right ventricle unless we suppose that the cardiac impulse reached the epicardial surface in this region abnormally late. This supposition would imply that the

where large diphasic or multiphasic P complexes are obtained) ordinarily yield ventricular deflections like those of leads from the left side of the precordium, and may, therefore, be considered semidirect leads from the surface of the left ventricle. It will be noted that the complexes of the unipolar dorsal lead (Lead D_{viii}) closely resemble those of Lead E_{35}.

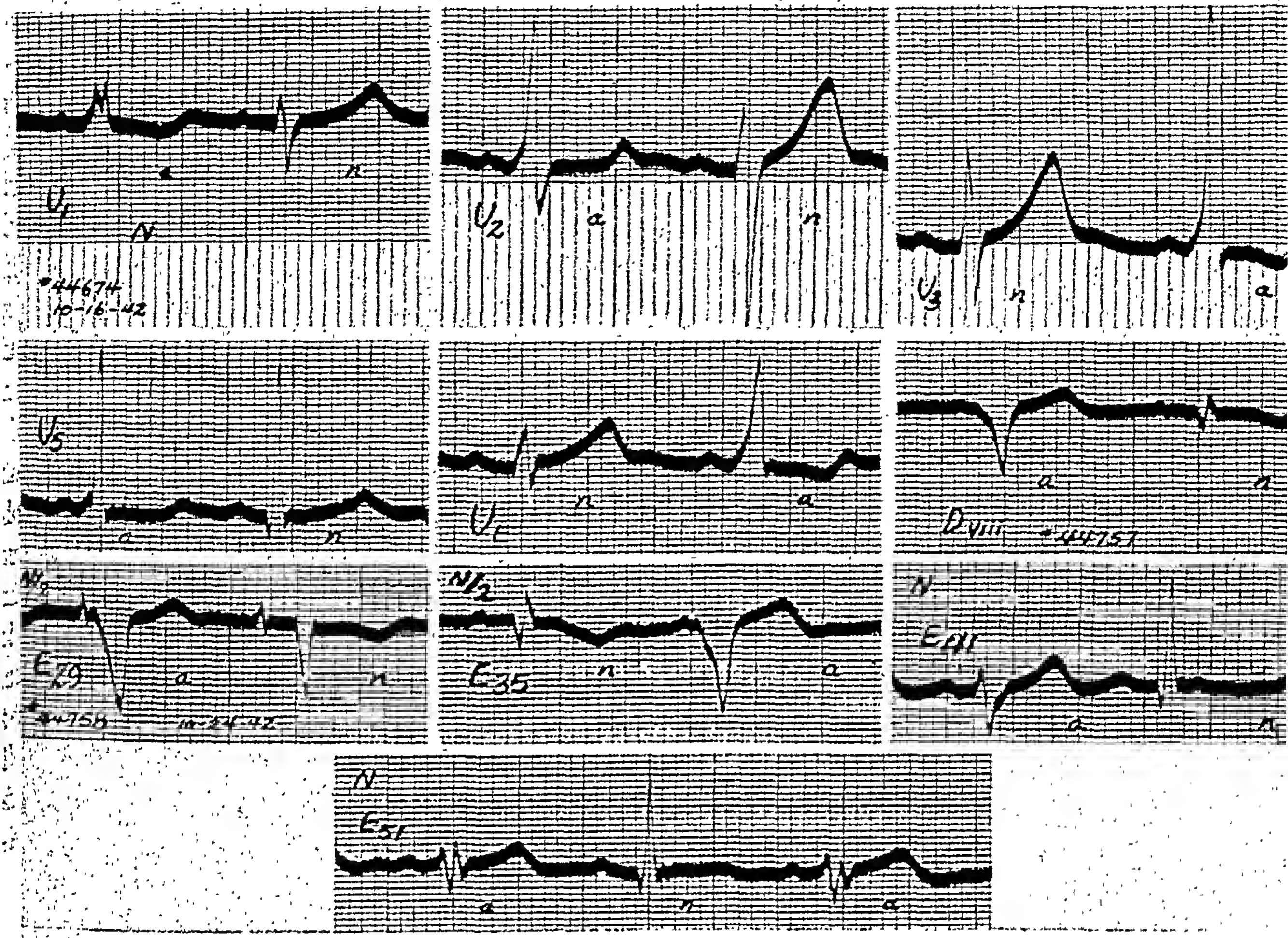

Fig. 2.—Case 1. Precordial Leads V_1, V_2, V_3, V_5, and V_E. A unipolar lead from the region of the eighth spinal process (D_{viii}). Four unipolar esophageal leads; these leads are labeled E, followed by a number which gives the distance (in centimeters) of the exploring electrode from the nares. Complexes labeled *a* are anomalous, those labeled *n*, normal. In this and in subsequent figures the symbol *N* indicates that the lead was taken with the electrocardiograph at the normal sensitivity (1 cm. equals 1 mv.) the symbol *N/2* indicates that the sensitivity was reduced to one-half the normal (1 cm. equals 2 mv.).

Despite these great differences in form between the normal and the anomalous ventricular complexes, measurements show that in many leads the two types of QRS groups are structurally related. We have already mentioned that the interval from the beginning of the P wave to the end of the QRS complex (the RS-T junction) is of the same length when atrioventricular excitation is anomalous as when it is normal. Measurements of the curves of Fig. 2 are in accord with this statement, and also show that the corresponding peaks of the chief QRS components of the two kinds of curves usually occur at approximately the same time in relation to the P wave. Table I gives, for each of the leads shown in Fig. 2, the intervals from the onset of P to (1) the onset of the initial

line (V_{3R}).* In the lead from the right midclavicular line (RMCL) the premature component is isoelectric. All of these leads were taken from points at the level of the cardiac apex.

In this instance the muscle activated prematurely must have been in the dorsal wall of the heart near the ventricular base, or in the neighboring part of the ventricular septum. This conclusion is supported by the following considerations:

a. The orientation of the electrical forces generated by the heart during the premature fraction of the QRS interval indicates that throughout that period the excitatory process was spreading from the dorsal toward the ventral, and from the basal toward the apical, parts of the myocardium. In this part of the cardiac cycle the potential of the auricular and subauricular† levels of the esophagus and that of a zone extending from the eighth dorsal spine around the right side of the chest to the right anterior axillary line were negative, whereas the potential of the ventricular levels of the esophagus and that of a zone extending from the right parasternal line across the precordium and around the left side of the chest to the left scapular line were positive.

b. The earliest fractions of the premature component of QRS are most conspicuous in the leads from the auricular and subauricular levels of the esophagus. This, together with the relatively large size of this component as a whole in these leads, suggests that when they were taken the exploring electrode was near the region where premature activation began. We believe, in other words, that this component is large in these leads for the same reason that the auricular deflections are large in them.

c. It has been pointed out that in all of the precordial leads the R wave of the anomalous is taller than that of the normal QRS complex. The anomalous QRS group has a net area that is algebraically larger, and the anomalous T complex a net area that is algebraically smaller, than that of the corresponding subdivision of the normal ventricular complex. In the esophageal leads the reverse is the case. This clearly indicates that anomalous excitation increased the number of muscle units activated in a dorsoventral direction.

*Leads from points on the right side of the chest similar in location to the points from which the standard precordial leads are taken are conveniently differentiated from these by adding R to the subscripts of the standard symbols of the leads to which they correspond.

In normal subjects and in cases of right ventricular hypertrophy, left ventricular hypertrophy, right bundle branch block, and left bundle branch block, the ventricular complexes of unipolar leads from the left posterior axillary line and the left scapular line (at the level of the cardiac apex) are usually similar to those of the leads from the left side of the precordium. Exceptions to this general rule occur in those cases in which the transitional zone is displaced to the left. In these the leads from the left side of the precordium display complexes intermediate in form between those of the leads from the right side of the precordium and those of the leads from the left back. The ventricular complexes of the latter are then like those usually seen in Leads V_5 and V_6 in the type of heart disease present. As a general rule the ventricular complexes of the leads from more lateral parts of the right anterior chest wall are similar to those of Lead V_1; exceptionally, they are like those usually present in this lead in cases of the kind being studied. The deflections of the leads from the right back are variable in form, but often resemble those of Lead V_R. The QRS complex is ordinarily minus-plus diphasic. In right ventricular hypertrophy the second phase usually has the greater voltage, and in left ventricular hypertrophy the first phase usually has the greater voltage. In right bundle block the second component is often very broad. In left bundle branch block the first or negative phase is usually the larger, and the second or positive phase may be absent.

†Less than 10 cm. below the point at which the largest auricular deflections were recorded.

right branch of the His bundle was not functioning, and is not supported by the character of the ventricular complexes of the other leads.

A complete set of the esophageal leads, taken when the cardiac mechanism was continuously anomalous, is reproduced in Fig. 3. The premature component of QRS is inconspicuous in Lead E_{15}; in Leads E_{18}, E_{21}, E_{24}, E_{27}, E_{29}, and E_{33} it is negative, and in the last four of these leads it is conspicuously large. The brevity of the P-R interval in the leads in which this component is largest is apparently due chiefly to the comparatively large magnitude of its earlier fractions; in some of the other esophageal leads these are inconspicuous or isoelectric. In Leads E_{36}, E_{39}, E_{42}, E_{45}, and E_{51} the premature component is positive and relatively small. It will be observed that the QRS complexes of the leads from the highest levels of the esophagus are the inverse of QRS complexes of the leads from the lowest levels. We have already noted that the latter display both an R and an R′ deflection, and are very different in form from the normal complexes of the same leads and from the anomalous complexes of the leads from the left side of the precordium.

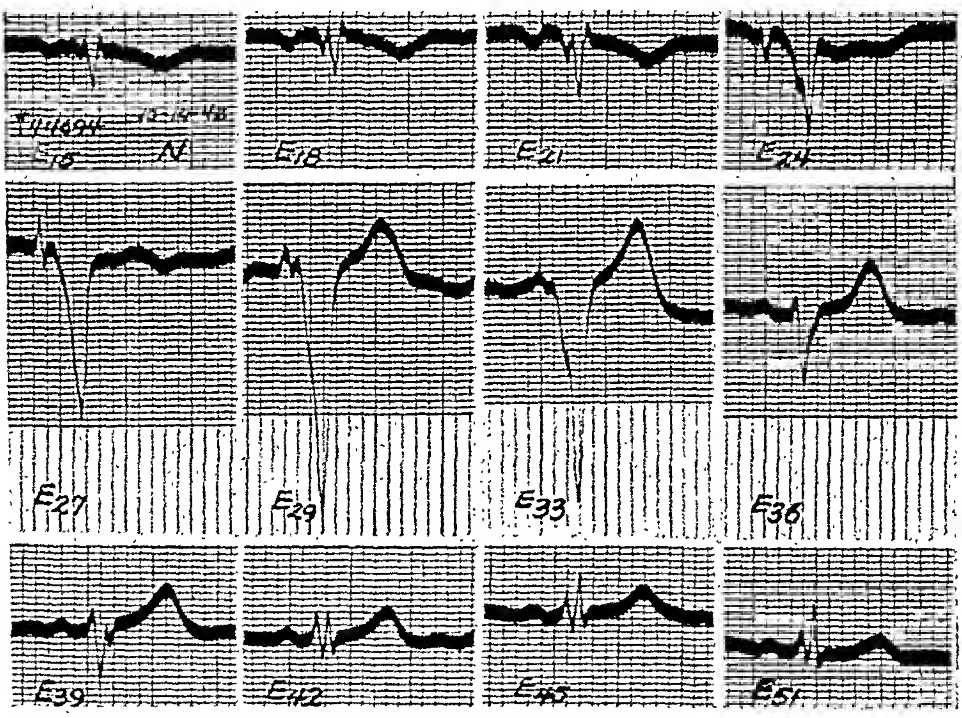

Fig. 3.—Case 1. Esophageal leads. The number which follows *E* gives the distance (in centimeters) of the exploring electrode from the nares.

Unipolar leads from the back and the anterolateral aspect of the right side of the thorax are shown in Fig. 4. The premature component of QRS is clearly negative in the leads from the eighth dorsal spine (D_{viii}), the right posterior axillary line (RPAL), the right midaxillary line (RMAL), and the right anterior axillary line (RAAL). It is clearly positive in the leads from the left midaxillary line (V_6), the left posterior axillary line (LPAL), the left scapular line (LScL), and a line midway between the right sternal margin and the right midclavicular

the initial component of the normal complex is likewise negative. Normally, the ventricular cavities are negative throughout the QRS interval, and the initial negative component of QRS in leads from the auricular and subauricular levels of the esophagus is presumably due to the transmission of the potential of the ventricular cavities to these regions. That anomalous atrioventricular excitation gives rise to initial negativity of the left ventricular cavity as a whole seems unlikely, for, in the leads from the left side of the precordium, the premature component of the anomalous QRS complex is positive even when the normal QRS complex displays a conspicuous Q deflection. The evidence bearing upon its effect upon the initial potential of the cavity of the right ventricle is less conclusive. In the leads from the right side of the precordium the premature component of the anomalous QRS complex is positive in Case 1, but not in all the other cases of our series. It would seem that positivity of this component in all of the standard precordial leads must be due to activation of the dorsal ventricular wall from without inwards or to dorsoventral activation of septal muscle, if we are warranted in excluding premature activation of the anterior ventricular wall on the grounds previously mentioned.

The occurrence of a second R summit in the anomalous QRS complex of Leads V_1 and V_{3R} is not easy to explain satisfactorily. If the first R summit, which corresponds, as regards its relation to P, to the normal R peak, marks the completion of the excitation of the anterior wall of the right ventricle by impulses arriving via the His bundle, the later fractions of the bifid R wave must be of septal origin in the sense that they represent the overbalancing of opposing forces by those generated by the activation of septal muscle in a left to right direction. In the leads from the left back and the left axilla, an S deflection occupies this same part of the QRS interval, and it is apparent that this deflection and the second R summit in question have the same origin. It seems likely that abnormally early activation of parts of the posterior and posterolateral wall of the left ventricle by the anomalous excitation process prevented the development in these regions of those electric forces which, late in the QRS interval, normally opposed the septal forces referred to.

It may be pointed out here that our observations are not in accord with any of those hypotheses which attribute the electrocardiographic features of the syndrome under consideration to an anomaly of conduction or of impulse formation affecting the right or left branch of the His bundle. An anomaly of this kind should give rise to a QRS pattern characteristic either of complete or of incomplete bundle branch block. Left bundle branch block decreases the size of the R deflection and enormously increases the area of the S wave in the leads from the right side of the precordium. Right bundle branch block does not greatly change the height of the R wave, but substantially decreases the net area of QRS in the leads from the left side of the precordium. It does not abolish Q waves in these leads in cases in which they are present when

d. The form of the QRS deflections in the leads from the lower subauricular and the higher ventricular levels of the esophagus suggests that the parts of the dorsal ventricular wall nearest the exploring electrode were activated earlier when excitation was anomalous than when it was normal (Fig. 2). In Lead E_{35} the normal QRS group displays a final R deflection; in the anomalous beat, R is wholly lacking. In Lead E_{41} the normal beat exhibits a prominent Q and a late R peak, whereas in the anomalous complex R is small and its peak falls in the premature part of the QRS interval (Table I). In Lead E_{51} the situation is similar except that here the anomalous QRS complex has an R′ in addition to the initial R wave. This R′ summit comes at the same time as the normal R peak of the same lead. Fig. 3 shows that it is embryonic in Lead E_{39} and progressively larger in the leads from lower levels, which suggests that it represents the response of some of the lowest portions of the dorsal ventricular wall to the normal excitation wave. The leads from the left back (Fig. 4, LPAL and LScL) exhibit QRS deflections of similar form, whereas the QRS complex of these leads is normally dominated by a late R deflection.

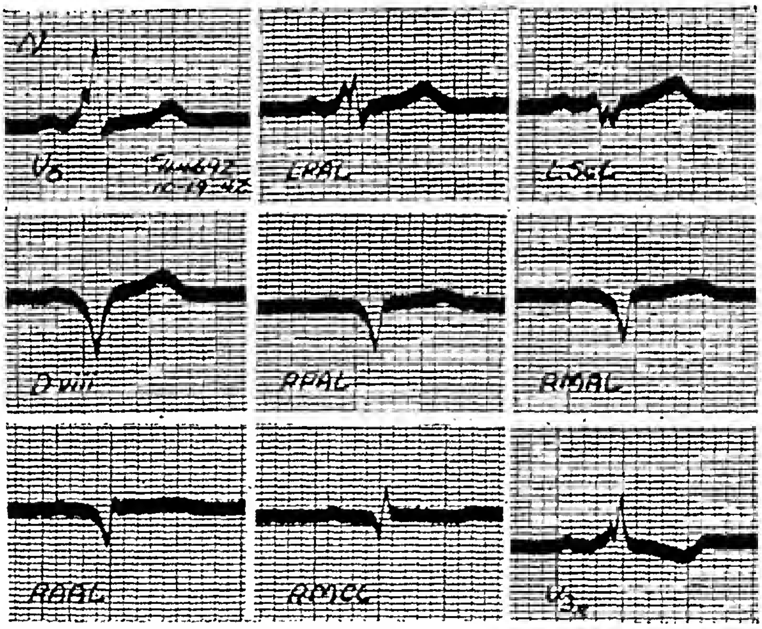

Fig. 4.—Case 1. Unipolar leads from the back and from the anterior right hemithorax at the level (approximately) of the cardiac apex. *LPAL*, left posterior axillary line; *LScL*, left scapular line; D_{VIII}, eighth dorsal spine; *RPAL*, right posterior axillary line; *RMAL*, right midaxillary line; *RAAL*, right anterior axillary line; *RMCL*, right midclavicular line; V_{3R}, halfway between the right midclavicular line and the right sternal margin.

It seems probable that the anomalous excitatory process invaded the subepicardial muscle first, and spread toward the endocardium, but lack of information as to what effects might be produced by dorsoventral activation of septal muscle makes it impossible to be sure that such was the case. The esophageal leads throw no light on the question as to whether the excitation wave spread through the dorsal ventricular wall from without inwards or vice versa. When the premature component of the anomalous QRS complex is negative in one of these leads,

atrioventricular excitation, and the electrocardiograms in half of our series of ten cases exhibit it. In the three cases of these five in which reversion of the anomalous ventricular complexes to the normal form was recorded in the limb leads, the mean electrical axis of the normal

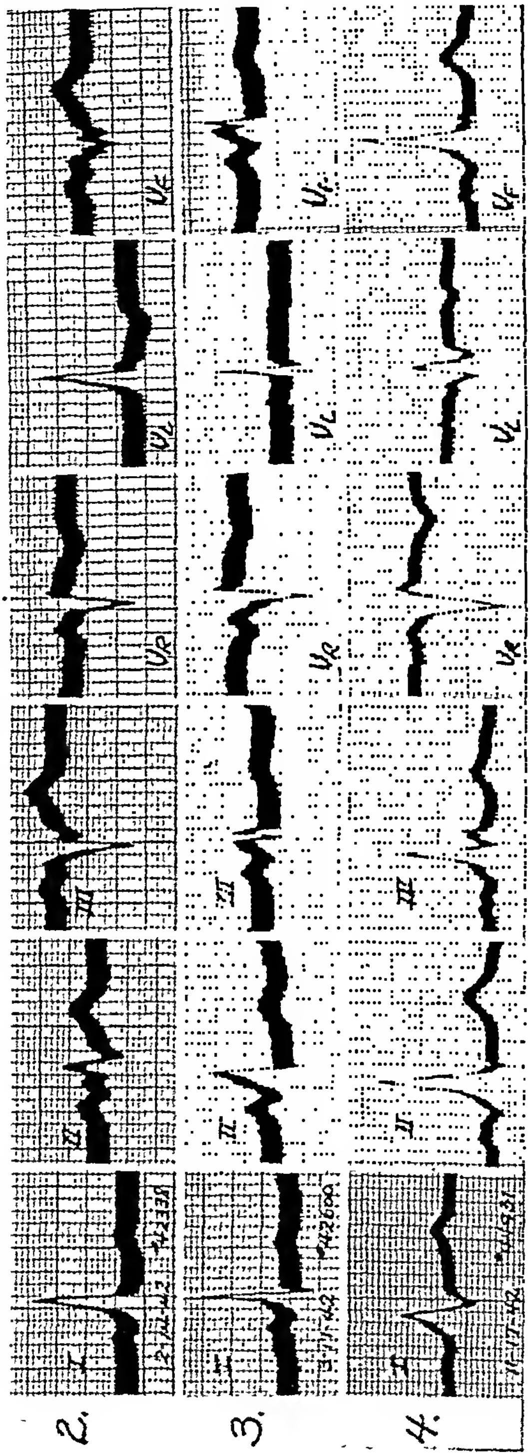

Fig. 5.—Cases 2, 3, and 4. Standard and unipolar limb leads.

QRS group is nearly vertical. It is clear, therefore, that the factors responsible for left axis deviation when the cardiac mechanism is anomalous are not the same as those that give rise to it when the cardiac

the ventricles are activated in the normal way. We feel sure, therefore, that an anomaly of the kind specified could not give rise to electrocardiograms of the kind reproduced in Fig. 2.

Classification of Cases; Groups A and B; the Electrical Axis.—As regards the form of the anomalous ventricular complex in certain leads, all the cases of our series are very much alike. With respect to the form of this complex in other leads, there are great differences between them. The leads from the left side of the precordium, particularly Leads V_4 and V_5, belong to the first class (Figs. 2, 6, 9, and 11). The anomalous QRS complex of these leads is always dominated by a large R wave, and the basal part of the ascending limb of this deflection is invariably slurred or notched by a positive premature component. In most instances there is also a small S wave in one or both of the leads mentioned, but Q is never present in either. In Lead V_6 the ventricular deflections have essentially the same form as in Leads V_4 and V_5, except that the voltage of R is almost always smaller, on occasion much smaller, as in Cases 2 and 4, and S is sometimes considerably deeper (Cases 1, 2, 3, and 4). Depending on the form of QRS in the leads from the right side of the precordium, particularly Leads V_1, V_2, and V_E, our cases have been divided into two groups: Group A, in which R is the sole, or by far the largest, deflection in all of these leads, and Group B, in which S or QS is the chief QRS deflection in at least one of them. Cases 1, 2, 3, 4, and possibly 7 fall in Group A (Figs. 2, 6, and 11), and Cases 5, 6, 8, and 9 fall in Group B (Figs. 9 and 11); Case 10, in which the form of QRS in these leads varied greatly, will be discussed separately. In the four cases in which esophageal leads were taken, the QRS complexes of the leads from the auricular and subauricular levels have essentially the same outline (Figs. 2, 3, 8, and 16). With one exception (Case 1), the ventricular deflections of the leads from the lowest levels of the esophagus are like those of the leads from the left side of the precordium. Leads from the back and the anterolateral aspect of the right side of the chest were taken in Cases 1, 3, 4, 8, and 10. In all of them the lead from the eighth dorsal spine exhibits a broad QS deflection similar to that seen in the leads from the auricular levels of the esophagus (Figs. 4, 7, and 8). The QRS complexes of the lead from the left scapular line resemble those of the leads from the left side of the precordium in only one instance. In most normal subjects, in bundle branch block, and in ventricular hypertrophy the complexes of the leads from the left back and those of the leads from the left side of the precordium are usually strikingly similar in form.

As to the limb leads, there are pronounced variations in the form of the ventricular complexes of Leads V_L and V_F, and therefore in the position of the electrical axis from case to case, but in Lead V_R the QRS deflections have approximately the same general outline in all instances (Figs. 1, 5, and 10). Left axis deviation is very common in anomalous

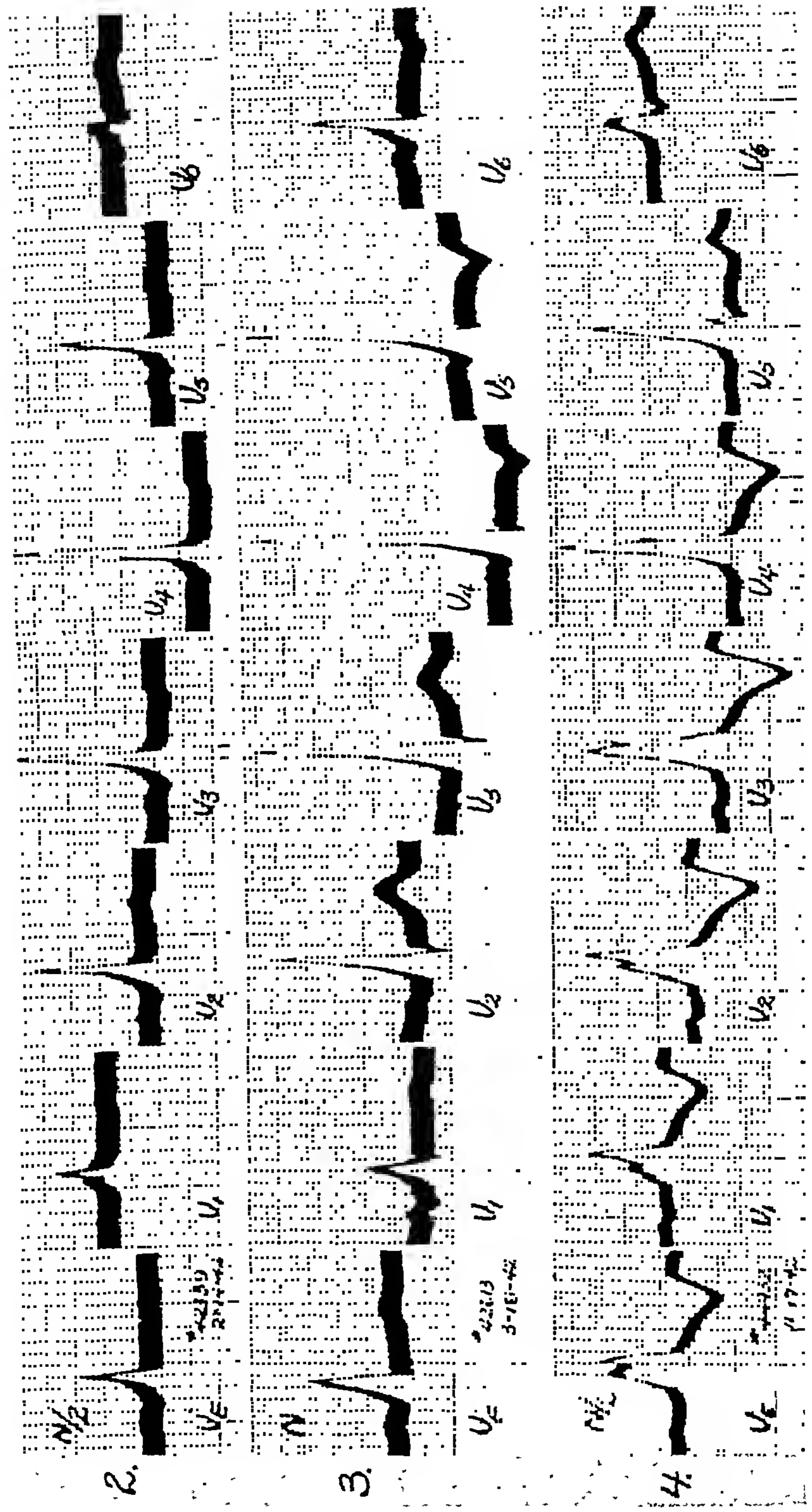

Fig. 6.—Cases 2, 3, and 4. Precordial leads.

mechanism is normal. In Case 1 the anomalous QRS deflections of Lead V_F (Fig. 1) resemble those of the leads from the ventricular levels of the esophagus (Fig. 3), although the initial R wave (not present in the strip of Lead V_F reproduced, but well marked in tracings taken on other occasions) is much larger in the esophageal leads. In Case 8 the ventricular deflections of Lead V_F (Fig. 10) are like those of the leads from the right side of the back (Fig. 7), and, in Case 6 (Fig. 10), like those of esophageal Lead E_{47} (Fig. 8). In these same cases, the QRS deflections, although not the T waves, of Lead V_L are more like those of the leads from the left side of the precordium. It seems probable, therefore, that the occurrence of left axis deviation was due in these cases to abnormally early excitation of the more basal parts of the dorsal ventricular wall and the transmission of the potential variations of this region to the left leg as in posterior myocardial infarction. In those instances in which the limb curves do not display left axis deviation, the ventricular complexes of Lead V_F are like those of the leads from the left side of the precordium or those of the leads from the lowest levels of the esophagus (Case 4, compare Lead V_F, Fig. 5, and Lead E_{59}, Fig. 8). Whether these cases differ from the others because the long axis of the heart made a more acute angle with the frontal plane, or for some other reason, is not clear. It should be noted that there is no correlation between the inclination of the mean electrical axis of QRS in the limb leads and the form of the anomalous ventricular complex in the leads from the right side of the precordium; left axis deviation occurs in cases that belong to Group A (Case 1, Fig. 1), as well as in those that belong to Group B (Case 8, Fig. 10). Our observations suggest, however, that cases of the first group are more likely to display prominent S waves in Lead I and in the leads from the extreme left side of the precordium than are those of the second.

Additional Cases of Group A; Comparison With the Type Case.—Cases 2, 3, 4, and 7 are members of Group A, and may be compared with the type case of this group which has been discussed at length. The anomalous ventricular complexes in Case 2 differ from those in Case 1 in the following respects: there is no S deflection in either Lead I or Lead V_L (Fig. 5); the R wave of Lead V_1 is less distinctly bifid; there is no S deflection in any of the precordial leads except Lead V_6, and the R wave of this lead is very small (Fig. 6).

In Case 3 the limb leads do not show left axis deviation (Fig. 5), and the R wave of Lead V_1 has only one peak (Fig. 6). Two sets of curves were taken in this case, the first on March 17, 1942, before splanchnicectomy, and the second on Aug. 17, 1943, after this operation. The extremity and precordial leads reproduced here belong to the first set, and the other thoracic leads, to the second set. The differences between the two sets of tracings are of a minor kind. Compared to the first, the second set of precordial curves exhibits a larger S wave in Leads V_1 and V_F, smaller R deflections in Leads V_2 to V_6, inclusive, and upright in-

doubt as to whether this case properly belongs in Group A. In the figures it has been placed with the cases of Group B.

In Case 4 precordial leads were taken Nov. 13, 1942, as well as on Nov. 17, 1942. There are no significant differences between the two sets of tracings. The form of the ventricular deflections of the standard leads, however, was quite variable, and could be greatly modified by forced respiration. There was always a prominent S wave in Lead I,

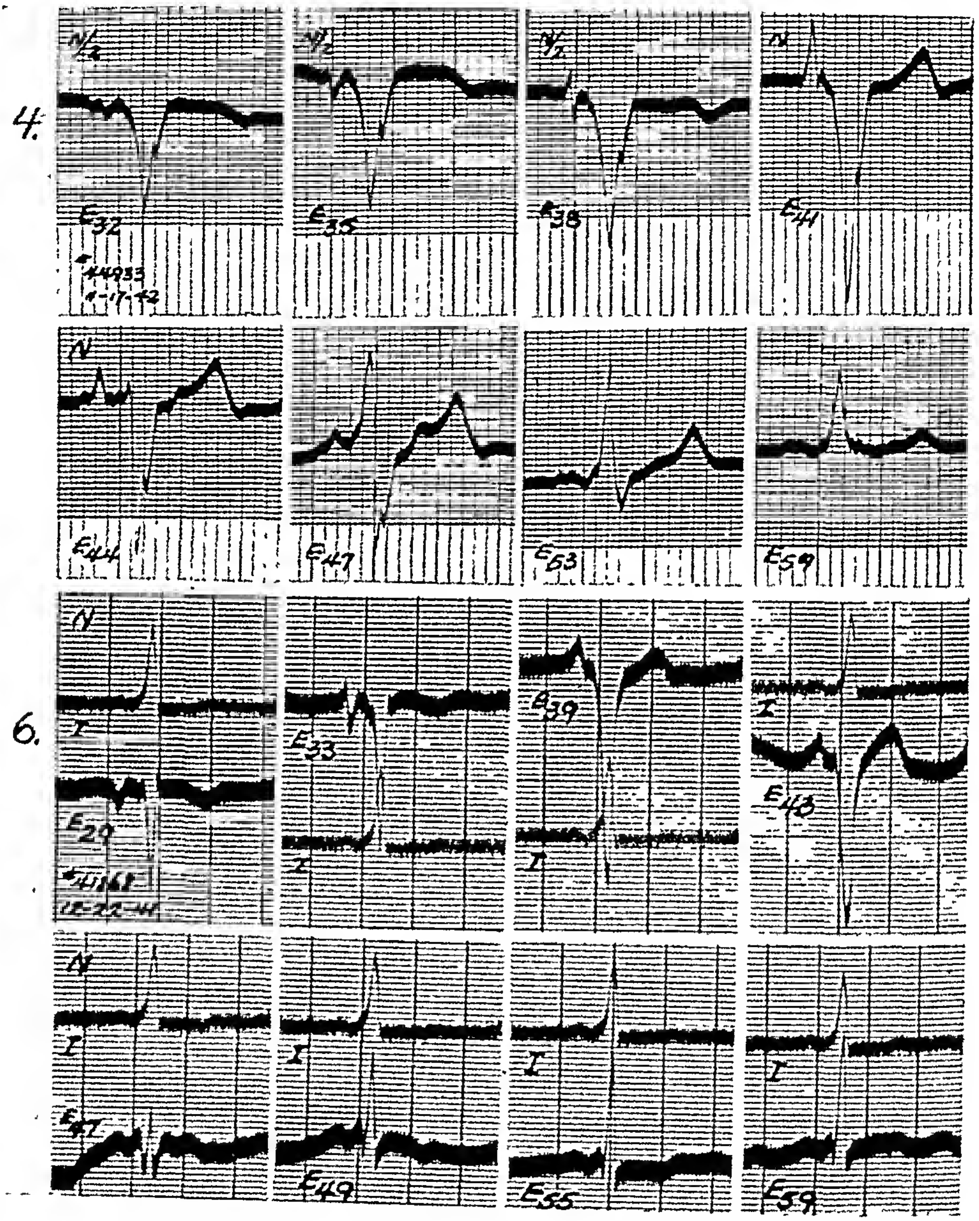

Fig. 8.—Cases 4 and 6. Unipolar esophageal leads. Compare with Fig. 3.

but in some records the voltage of R_1 is more than twice as great as in that reproduced (Fig. 5). The very long QRS interval, which measures at least 0.16 second, and the broad, deformed P waves of the limb leads raise the question as to whether anomalous atrioventricular excitation

stead of inverted T waves in Leads V_4, V_5, and V_6. The first set of leads from the back, the right axilla, and the right anterior chest wall differs from the second set in these particulars: there is a distinct S deflection in the lead from the left posterior axillary line, the T wave in this lead is inverted instead of upright, and there is no S in Lead V_{3R}.

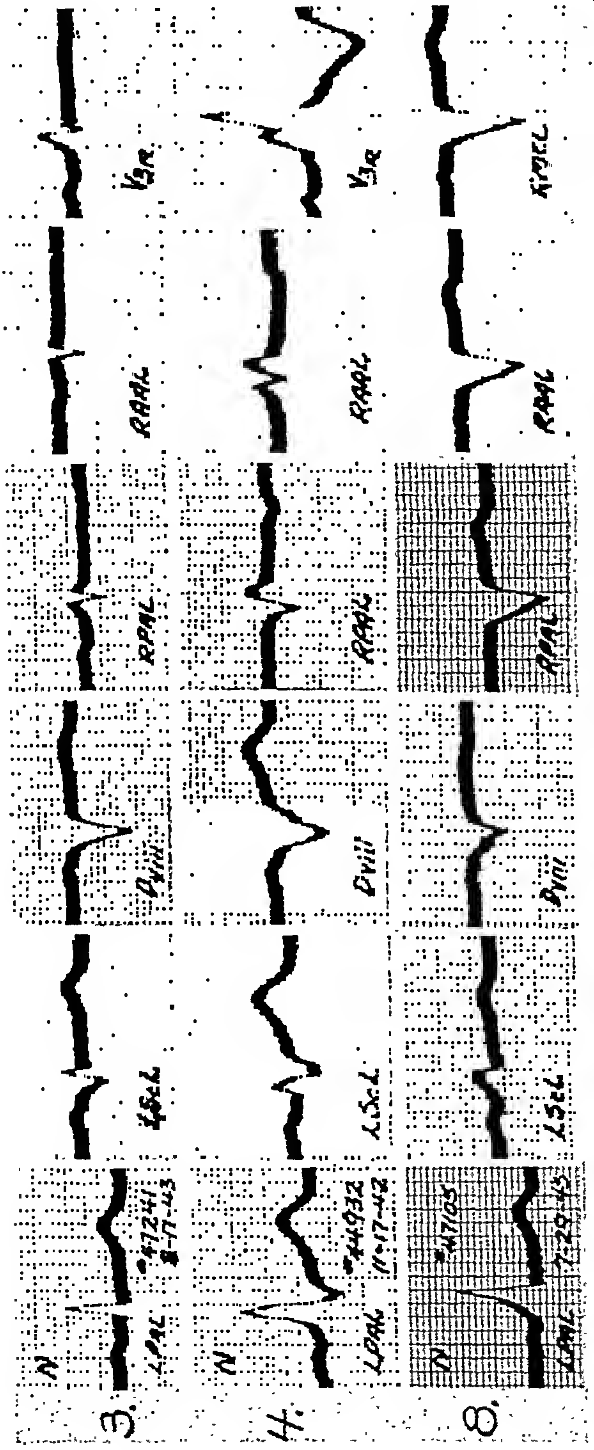

Fig. 7.—Cases 3, 4, and 8. Unipolar leads from the back and right anterior hemithorax. Compare with Fig. 4, in which the same symbols are employed.

In Case 7 precordial leads were taken on three occasions, June 19, 1934, July 9, 1934, and July 27, 1934. The second set of curves is reproduced (Fig. 11). In the others the ventricular complexes of Lead V_E have the same form, but those of Lead V_1 display a conspicuous S wave. In the third set this S is as large as the R wave, and there is some

ponent which is such a prominent feature of the anomalous QRS of Lead V_1 in the type case of Group A. It may be pointed out, however, that in Leads V_1 and V_2 the net area of the anomalous QRS is algebraically larger than the net area of the normal QRS. This is clearly

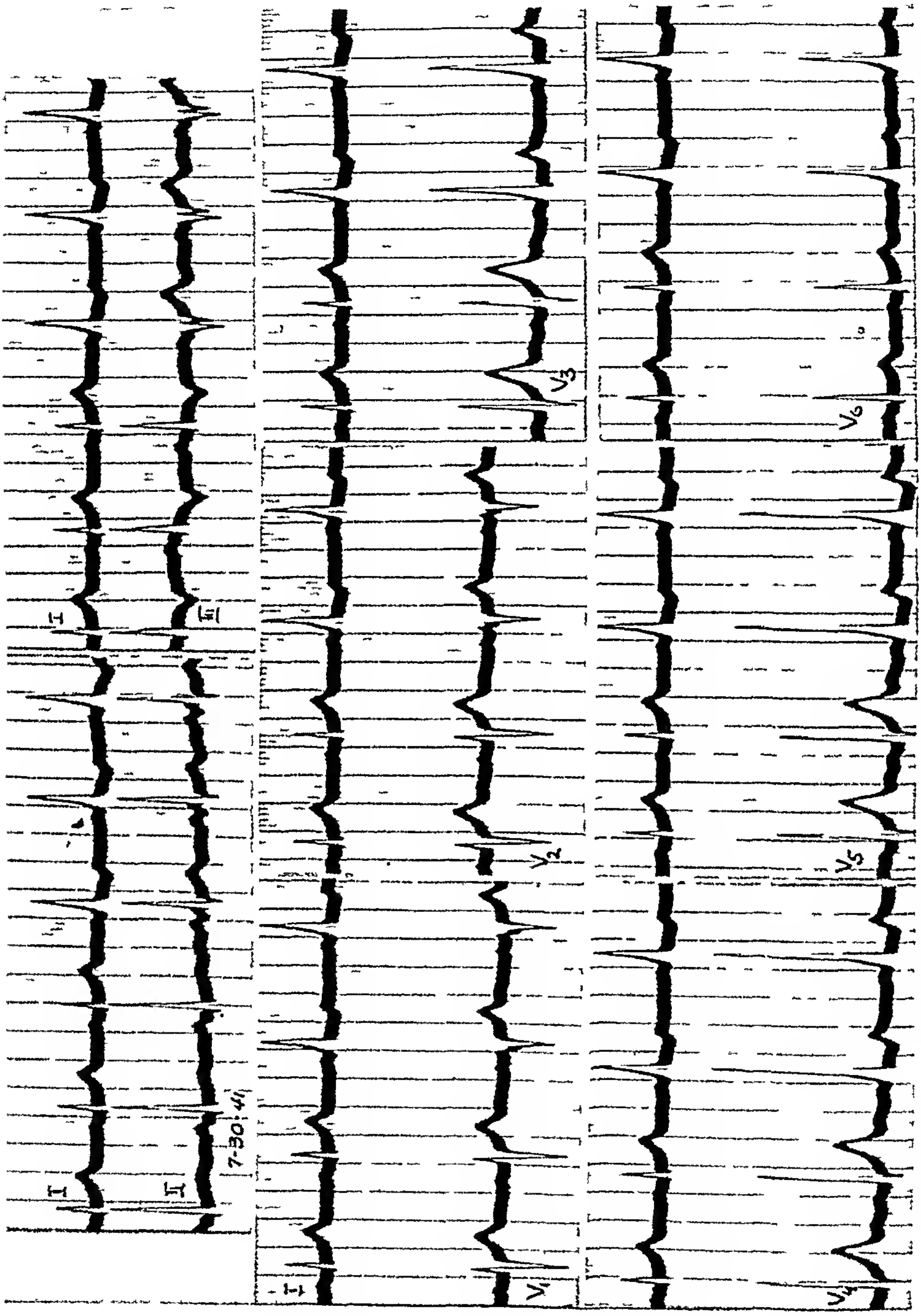

Fig. 9.—Case 5. Leads II and III and precordial Leads V_1 to V_6 inclusive, taken simultaneously with Lead I. In the records of the standard leads, the first three complexes are normal, the last three anomalous; in the precordial leads the first two are normal, the last two anomalous. Compare with Figs. 1 and 2.

indicated by the comparative size of the anomalous and the normal T waves. The difference between Case 5 and Case 1 in this respect is one of magnitude and not one of kind.

was the only cardiac abnormality present. The ventricular complexes of the thoracic and esophageal leads differ from those of the corresponding leads in the type case in minor particulars only (Figs. 6, 7, and 8). The premature component of QRS is positive instead of negative in the leads from the right anterior axillary line, and there is a more conspicuous final R deflection in the leads from the right back (Fig. 7). In the leads from the lowest levels of the esophagus (Fig. 8) there is only one R wave and this component is much larger than in Case 1 (Fig. 3).

The Type Case of Group B.—Case 5 is a typical example of the cases of the second group. In this instance transitions from the normal to the anomalous cardiac mechanism could be induced by the Valsalva procedure. Strips of the standard extremity leads and the unipolar precordial leads which show both kinds of ventricular complexes are reproduced in Fig. 9. No other leads were taken. Both the normal and the anomalous ventricular complexes of the limb leads closely resemble the corresponding complexes of the same leads recorded in Case 1. It will be noted, however, that in Lead I there is no S component in either species of complex, whereas, in Case 1, there is a conspicuous S in both (Fig. 1). There are no significant differences between the type cases of the two groups as far as the deflections of the leads from the left side of the precordium are concerned, with one possible exception. In Case 1 there is a conspicuous S wave in the anomalous QRS group of Lead V_6; in Case 5 this component is absent. On the other hand, the two cases differ greatly as regards the form of the anomalous ventricular complexes of the leads from the right side of the precordium (V_1 and V_2). In Case 5 the premature component is diphasic in Lead V_1 and very small in Lead V_2. There is a notch on the descending limb of the deep S wave of these leads. There is no trace of the final positive com-

TABLE II

CASE 5. INTERVALS IN FIG. 9. MEASUREMENTS IN SECONDS

	1		2		3		4		5	
LEAD	a	n	a	n	a	n	a	n	a	n
I	.122	.160	-	.173	.203	.203	-	.227	.244	.238
II	.115	.155	-	.170	.204	.204	.230	.237	.256	.251
III	.121	.152	.170	.170	.196	.202	.216	.234	.250	.248
V_1	.116	.150	-	-	.144 .182*	.175	.206	.204	.256	.244
V_2	.116	.166	-	-	.146 .187*	.192	.216	.222	.261	.262
V_3	.127	.172	-	-	.216	.210	.251	.232	.268	.266
V_4	.129	.171	-	.171	.211	.215	.250	.231	.257	.253
V_5	.128	.163	-	.171	.212	.204	.246	.228	.258	.252
V_6	.119	.155	-	.166	.206	.200	-	.238	.252	.232

Key:
a—anomalous; n—normal.
Column 1—measurement from beginning of P to beginning of QRS.
Column 2—measurement from beginning of P to peak of Q.
Column 3—measurement from beginning of P to peak of R.
Column 4—measurement from beginning of P to peak of S.
Column 5—measurement from beginning of P to end of QRS.
*Measurement to submerged R peak on descending limb of S.

normal, and that of the anomalous, eomplex bear the same relation to the P wave within a few thousandths of a seeond. In the leads from the right side of the preeordium the noteh on the deseending limb of S in the anomalous eomplex eorresponds in time to the peak of R in the normal QRS complex. These measurements, like those of Table I, support the view that the His bundle transmitted impulses when the eardiac meehanism was anomalous as well as when it was normal.

Group B; Additional Cases.—Case 6 is a much less striking example of Group B than that taken as the type. The S deflection is large in Leads V_1 and V_E, and there is no trace of a positive QRS eomponent at the end of the QRS interval (Fig. 11). On the other hand, the premature eomponent of QRS is positive in both of these leads, and there is a small S defleetion in Lead V_6. The ventrieular eomplexes of the leads from the lowest levels of the esophagus are similar to those of the leads from the left side of the preeordium (Fig. 8).

In Case 8 the premature eomponent is positive in all the precordial leads and there is a trace of a final upward defleetion in the QRS eomplexes of Leads V_1 and V_2 (Fig. 11). There is, however, no S wave in Lead V_6, and the chief QRS deflection is downward in Leads V_1 and V_E. The QRS eomplexes of the leads from the right baek, right axilla, and the right side of the anterior chest wall are quite different from those of the same leads in the eases of Group A (Fig. 7). The premature eomponent is negative in all of these leads, and there is no final R wave in any of them. These differenees are mentioned, but since these leads were not taken in any of the other eases of this group, they may not be significant.

In Case 9 there is a very deep QS defleetion in Lead V_1, and a deep S deflection in Leads V_2 and V_3 (Fig. 11). The premature eomponent is negative in the first of these leads and positive in the other two. There is no traee of a final R defleetion in either Lead V_1 or V_2, and there is no S wave in Lead V_6. This case presents all the characteristics of the group.

It will be noted that there is no S deflection in Lead I in any of the eases of Group B, although the position of the mean electrieal axis of the anomalous QRS eomplex varies greatly from case to case. The absence of a prominent S wave in Lead V_6 is also conspicuous (Figs. 9 and 11). Although we suspect that the muscle on the dorsal wall of the heart that was activated prematurely was smaller in amount or different in distribution in the eases of this group than in those of Group A, there is not enough evidenee bearing on this point to justify any conclusion. We must, therefore, consider whether the electrocardiographie differenees between the cases of these two groups are dependent upon differences in the order of ventrieular activation or upon variations in the position of the heart. The magnitude of the differenees, as regards the form of the anomalous ventricular complexes of the leads from the right side of the precordium, between Cases 1 and 4, on the one hand, and Cases 5

Table II gives, for each lead and for each type of complex, measurements of the interval from the beginning of the P wave to (1) the onset of the first QRS deflection, (2) the apex of Q, when this component is present, (3) the apex of R, (4) the apex of S, and (5) the end of the QRS complex. The P-R interval of the anomalous beats appears to be

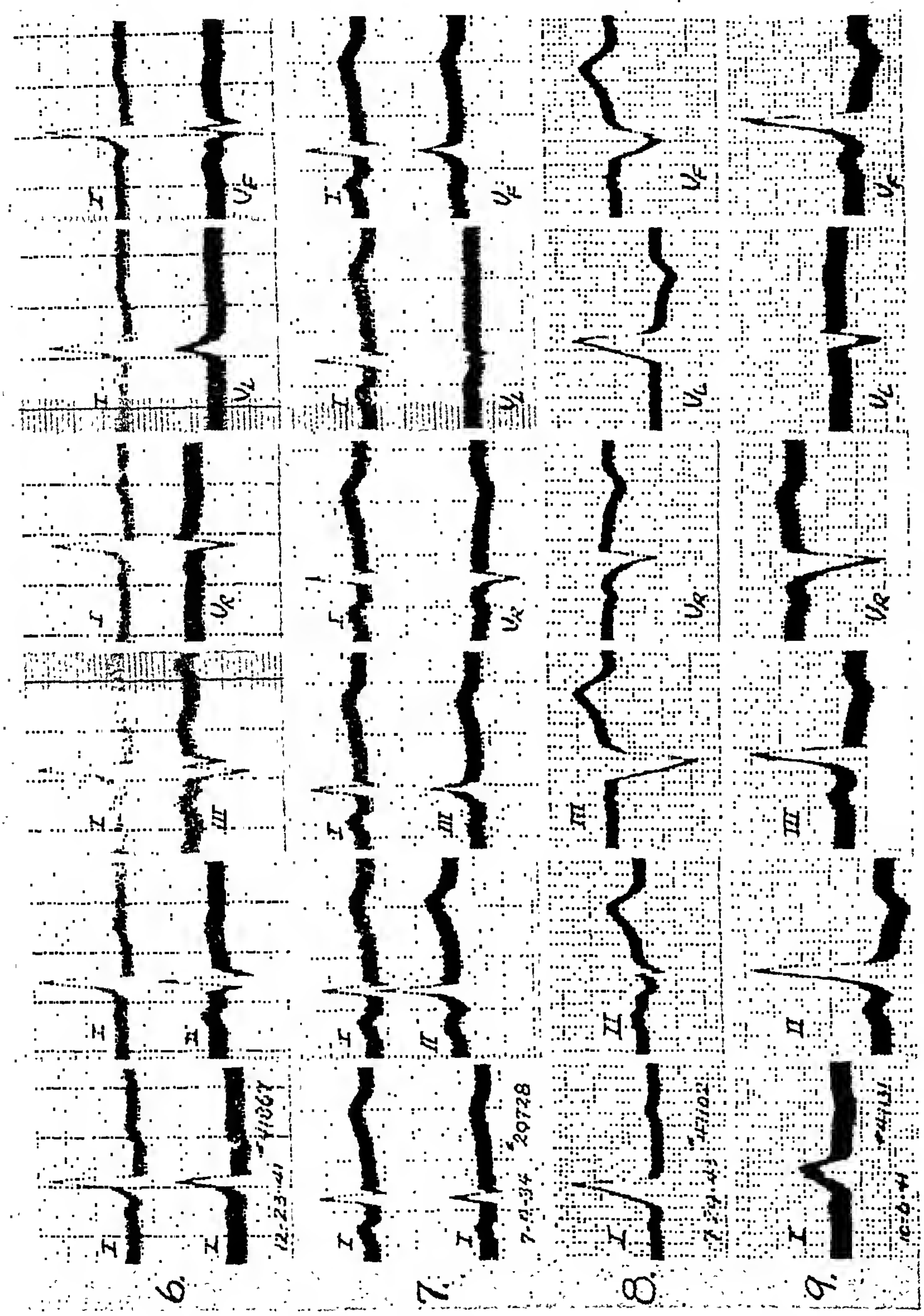

Fig. 10.—Cases 6, 7, 8, and 9. Standard and unipolar limb leads. Compare with Fig. 5.

roughly 0.04 second shorter than that of the normal beats, and the interval from the beginning of P to the end of the QRS complex is approximately the same for beats of both types. In the standard limb leads and in the leads from the left side of the precordium the R peak of the

and 9, on the other, is *certainly opposed to the second supposition.* This difference is particularly striking when it is borne in mind that, as regards the form of the normal ventricular complexes, Cases 1 and 5 differ only in very minor particulars. We must, however, remember that the effect produced by the position of the heart upon the ventricular deflection must be dependent upon the character of the potential variations on the different aspects of the ventricular surface, and, consequently, that a given change in the position of the heart may give rise to conspicuous changes in the ventricular electrocardiogram, or no changes at all, depending upon the epicardial distribution of potential variations of one kind, as compared to the distribution of those of an opposite sort. On the basis of the data presented, it is not possible to accept or reject either of the two possibilities mentioned, but the observations described in a later section of this article indicate that the differences between the cases of Group A and those of Group B are due, at least in some measure, to differences in the order of ventricular activation.

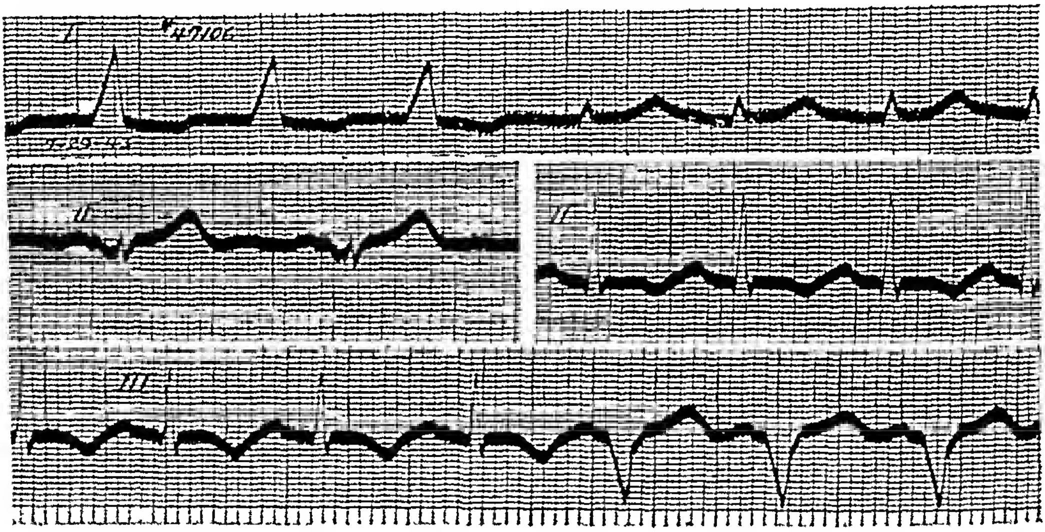

Fig. 12.—Case 8. Leads I, II, and III, showing both anomalous and normal complexes.

OBSERVATIONS RELATING TO THE EFFECT OF ATRIOVENTRICULAR RHYTHM UPON THE FORM OF THE VENTRICULAR COMPLEX IN ANOMALOUS ATRIOVENTRICULAR EXCITATION

An accessory atrioventricular bundle, if it is regarded as a separate and distinct structure, and in no sense as a part of, or as connected with, the specialized atrioventricular system of the normal heart, can hardly transmit the excitatory process from auricles to ventricles when the cardiac rhythm is under the control of a center in the lower levels of the atrioventricular node. Our working hypothesis, then, implies that in cases of anomalous atrioventricular excitation the ventricular complex must assume the normal form on the induction of atrioventricular rhythm of the kind in which ventricular excitation is simultaneous with, or precedes, auricular. We have not made an extensive search of the

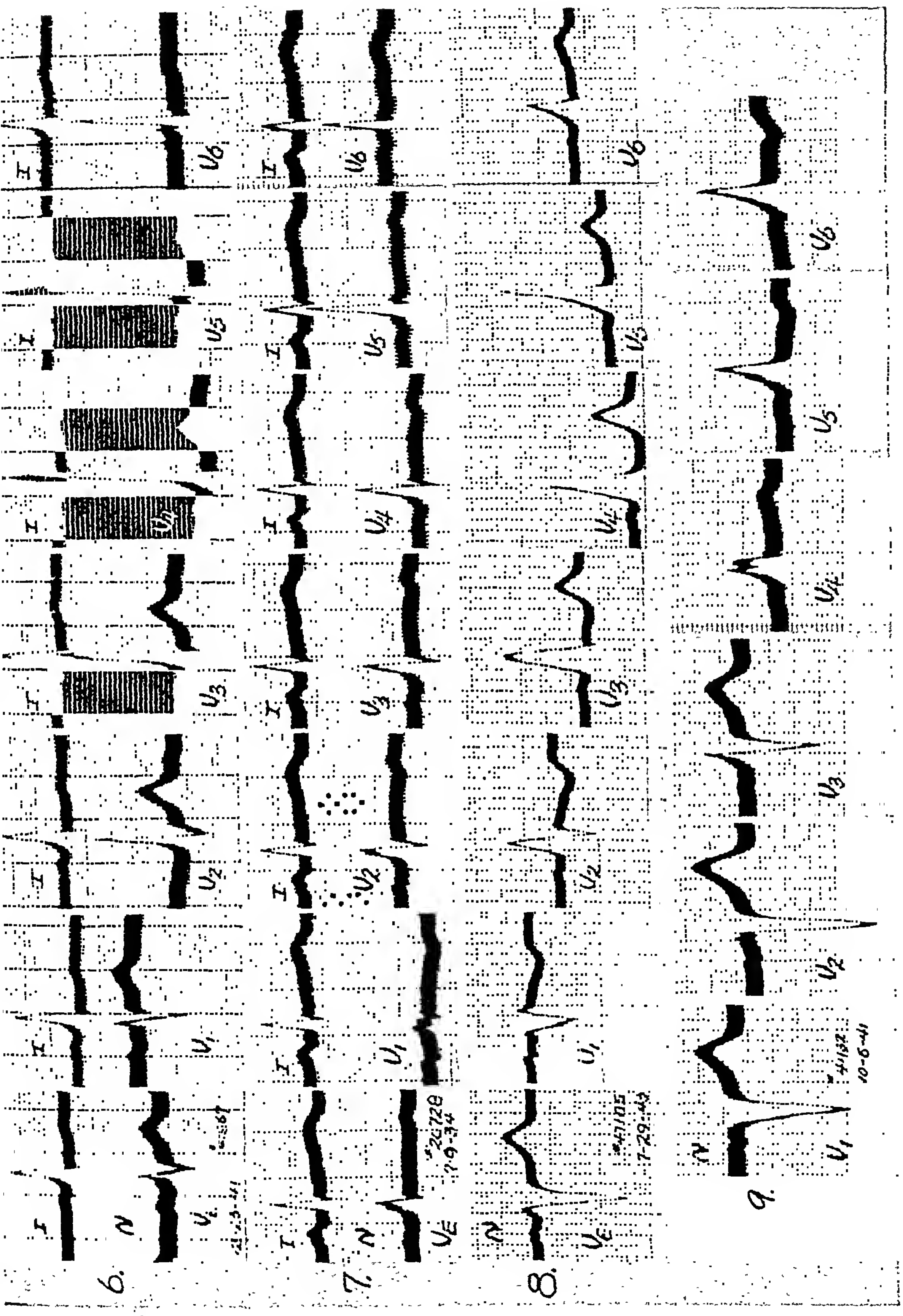

Fig. 11.—Cases 6, 7, 8, and 9. Precordial leads. Compare with Fig. 6.

P wave is followed by a slowly rising segment which is apparently part of the QRS complex. If this interpretation is correct, the QRS interval measures approximately 0.14 second, but if the segment in question is ignored, this interval does not much exceed 0.10 second. The abnormally long Q-T interval may be due to the administration of quinidine. The next two strips of record show a transition from sinus rhythm to atrioventricular rhythm. During this transition the ventricles were responding to the atrioventricular node, but some fraction of the auricular muscle was still responding to the sinus node, for that part of the P wave which remains visible retains its original form. In the fourth strip of record, no part of the P wave can be seen, and we may assume that when this record was taken all of the cardiac muscle was responding to the atrioventricular node. The final strip of record represents the re-establishment of sinus rhythm. The ventricular complexes recorded during the ectopic rhythm differ significantly from those of the control tracing in two respects: they display a somewhat shorter QRS interval and a definite Q deflection. It will be noted that Q did not appear as long as any trace of the original P wave preceded the QRS complex, and the reason for this is obvious. On the other hand, the reduction in the size of S which occurred simultaneously with the appearance of Q is difficult to understand. If it were due to the change in the location of the ventricular pacemaker it should have occurred when the ventricle began to respond to the atrioventricular node. It is probable that the change in the size of this component has no important significance, for it did not occur when atrioventricular rhythm was induced by carotid sinus stimulation after the administration of atropine.

The results of this experiment are somewhat equivocal, for the ventricular complex neither retained its original outline nor assumed an entirely normal appearance when atrioventricular rhythm developed. We have already mentioned reasons for suspecting that anomalous atrioventricular excitation was not solely responsible for all of the electrocardiographic peculiarities in this case. We do not, therefore, feel justified in concluding that the ectopic rhythm failed to abolish those that can be justifiably ascribed to it.

A most interesting case, the last of our series, and one of those studied by Hecht, at the William J. Seymour Hospital, remains to be described. The patient was under observation for a long period, and many electrocardiograms were taken. We shall describe and illustrate only the more significant.

The anomalous QRS complexes of the limb leads (Fig. 15, *a* and *b*) and those of the leads from the left side of the precordium (Leads V_4, V_5, and V_6, Fig. 14) have the same general contour in all records. The former exhibit pronounced left axis deviation, and the latter differ in no significant way from the QRS complexes of the same leads in the other cases of our series. On the other hand, the form of the QRS complexes of the leads from the right side of the precordium is very variable (Fig.

literature, but two cases of anomalous atrioventricular excitation in which atrioventricular rhythm of this sort was observed have come to our attention. One of these was reported by Fox, Travell, and Molofsky,[14] and the other by Aixalá.[15] The ventricular complex was of the normal form during the atrioventricular rhythm in both of these cases. The authors who reported them did not comment upon the possible significance of their observations on this point.

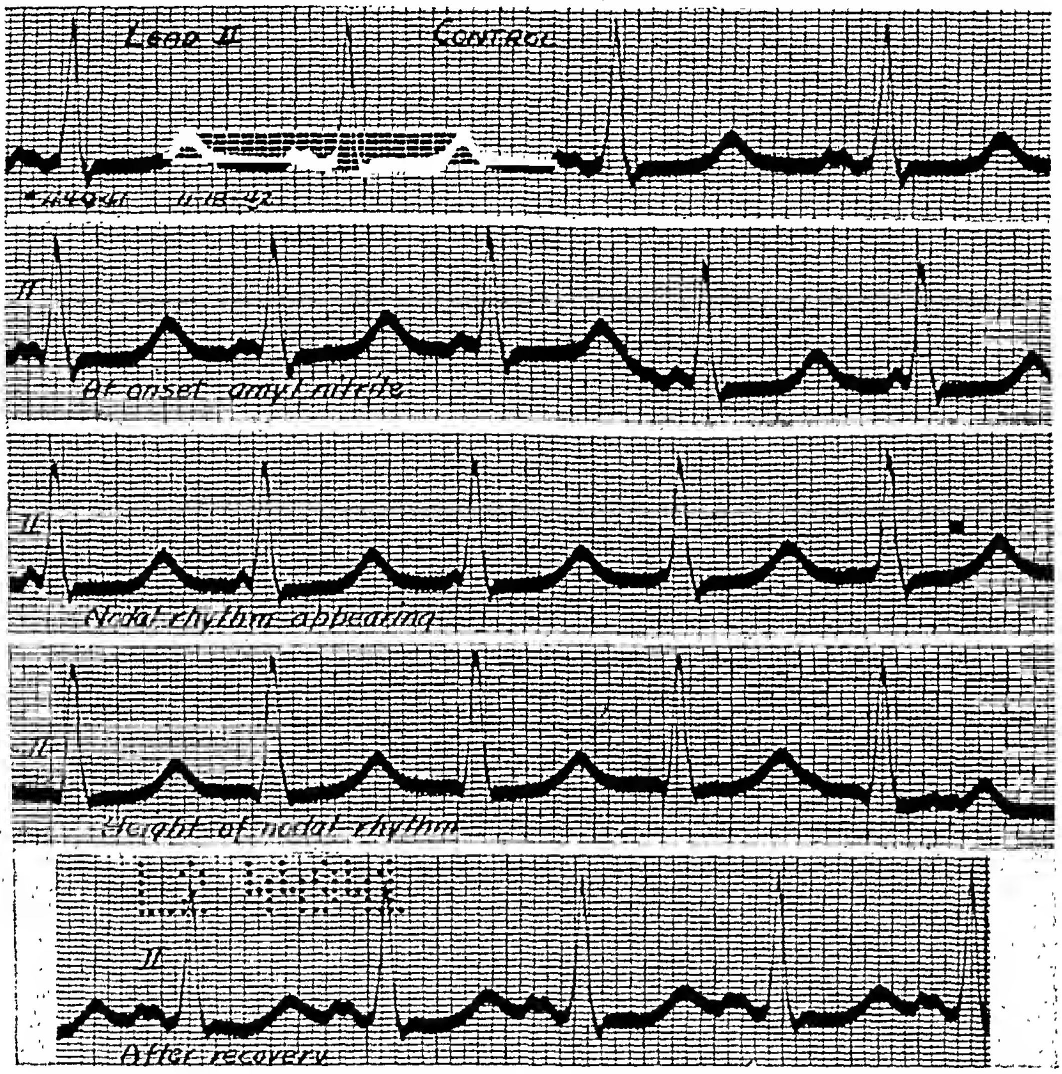

Fig. 13.—Case 4. The effect of atrioventricular nodal rhythm upon the form of the anomalous ventricular complex in Lead II.

In Case 4 of our series, atrioventricular rhythm of the kind in which the P wave is buried in the QRS complex was observed on two occasions. On the first, it appeared when the patient inhaled amyl nitrite approximately three hours after the administration of 0.6 Gm. of quinidine sulfate. Up to that time the latter had had no noticeable effect upon the cardiac mechanism. On the second occasion it was induced by carotid sinus stimulation approximately eight minutes after the hypodermic injection of 0.0013 Gm. of atropine sulfate. Thirty minutes after this injection the same procedure was no longer effective. The occurrence of atrioventricular rhythm after the inhalation of amyl nitrite is illustrated in Fig. 13. In the control record a broad, notched

14). In the tracing taken March 5, 1941, Leads V_1, V_2, and V_3 display large QS deflections, notched in the last of these leads by an embryonic R wave near the end of the QRS interval (Fig. 14, *a*). In the limb leads of the same date the P waves differ from those of the first electrocardiogram, dated Feb. 27, 1941, in that they are small in Lead II and inverted in Lead III. The curves of Nov. 3, 1941 (Fig. 14, *b*), show a large QS deflection in Lead V_1 and a polyphasic QRS complex in Lead V_2. In the other precordial leads QRS is represented by a broad R wave, slurred at the base of its ascending limb. Esophageal tracings taken on the same date show large QS deflections in the lead from the auricular level, and complexes like those of the leads from the left side of the precordium in Leads E_{10} and E_{50}. In the records of Dec. 31, 1943 (Fig. 14, *c*), the chief QRS deflection is upward in all of the precordial leads, including V_E; in the leads from the left side of the precordium the R waves are much taller than in the previous records, and the T waves are inverted. It is unlikely, if not impossible, that these pronounced variations in the form of the ventricular complexes of the precordial leads could have been due solely to variations in the position of the heart or to errors in placing the exploring electrode.

By Dec. 29, 1943, the patient's mental condition had deteriorated to such an extent that it was necessary to administer sodium amytal in a dose of 0.25 Gm. (3¾ grains) to obtain satisfactory electrocardiograms. In some of the records taken on that day, and subsequently, the P deflections are upright in all of the standard limb leads; in others they are inverted in Leads II and III (Fig. 15, *a* and *b*). We shall assume that P waves of the first type represent normal sinus rhythm, and those of the second type, a homogenetic rhythm arising in the upper levels of the atrioventricular node. Whether or not this assumption is justifiable is of no consequence, if it is admitted that the centers responsible for the two rhythms differed in location. Unfortunately, one rhythm can be distinguished from the other only in Lead II, Lead III, or a lead from the auricular levels of the esophagus. We are, therefore, not able to say whether or not the variations in the form of the ventricular complexes exhibited by the records we have already described were due to variations in the location of the cardiac pacemaker. We mention this because other records show clearly that the character of the auricular rhythm exerted an important influence upon the form of the ventricular deflections of the leads from the right side of the precordium. It had only minor effects upon the outline of these deflections in the other leads employed.

On Dec. 29, 1943, a rather extensive exploration of the potential variations of the thorax was carried out. In the limb leads of that date the P wave is inverted in Leads II and III, but it is not certain that atrioventricular rhythm was continuously present during the period required to take all of the many unipolar leads employed. In the leads from the left margin of the sternum, from the left midclavicular line, and from

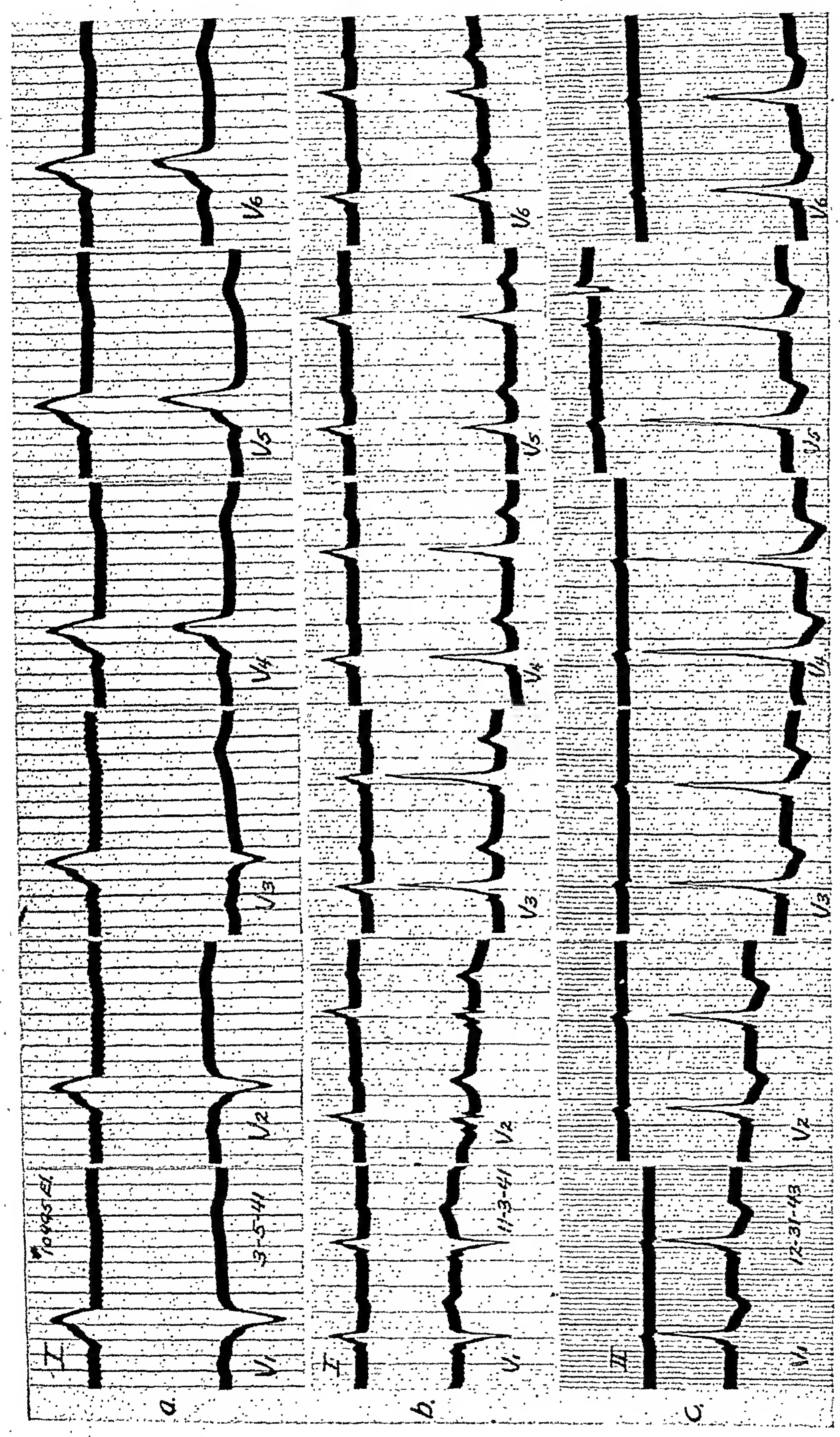

Fig. 14.—Three sets of precordial leads taken simultaneously with a standard limb lead. In *c* the limb lead was taken with the electrocardiograph at subnormal sensitivity. Note variation in the form of the ventricular complexes of the precordial leads.

the lead taken with the exploring electrode in the fifth intercostal space at the right sternal margin, the ventricular complex is of the same form as in the leads taken from points farther to the left. In the other leads the R component is largest in comparison with the Q deflection in those from the second intercostal space, and is either smallest or absent in those from the fifth intercostal space. In the leads from the right mid-axillary line and right anterior axillary line (level of the fourth and

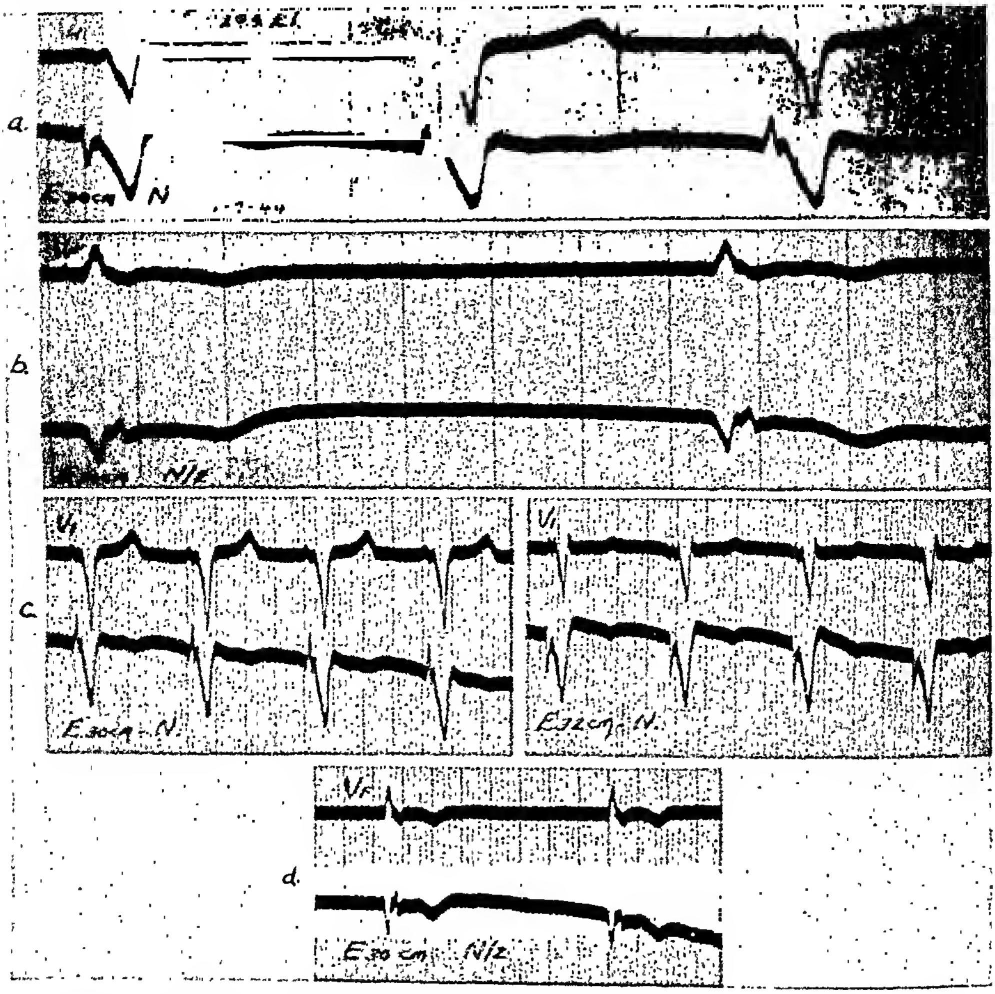

Fig. 16.—Case 10. *a*, Transition from atrioventricular rhythm arising in the upper levels of the atrioventricular node to sinus rhythm; precordial Lead V_1 taken simultaneously with a lead from the auricular level of the esophagus. *b*, Taken after neo-synephrin on Jan. 7, 1944. Two beats which arose in the lower levels of the atrio-ventricular node (QRS followed by a P wave); lead from the auricular level of the esophagus taken simultaneously with Lead V_F. *c*, Lead from the auricular level of the esophagus taken simultaneously with precordial Lead V_1; the first strip shows sinus rhythm, the second a rhythm arising in the upper levels of the atrioventricular node. *d*, same as *b*, but with camera running at a slower speed.

fifth intercostal space), the QRS complex is represented by a QS deflection. In the leads from the left posterior axillary line and the left midscapular line (level of the fifth intercostal space), the QRS complexes are like those of the leads from the left side of the precordium. In the lead from the left paravertebral line, at the same level, QRS consists of a broad R, followed by a small S wave. In

a line halfway between the two (levels of the second, third, fourth, and fifth intercostal spaces), the QRS deflections are represented by a broad R wave which is slurred near the base of its ascending limb. In the leads from the right sternal margin, the right midclavicular line, and a line midway between the two (levels of the second, third, fourth, and fifth intercostal spaces), the QRS complex consists of a broad QS deflection, or of a Q followed by an R wave, with one notable exception. In

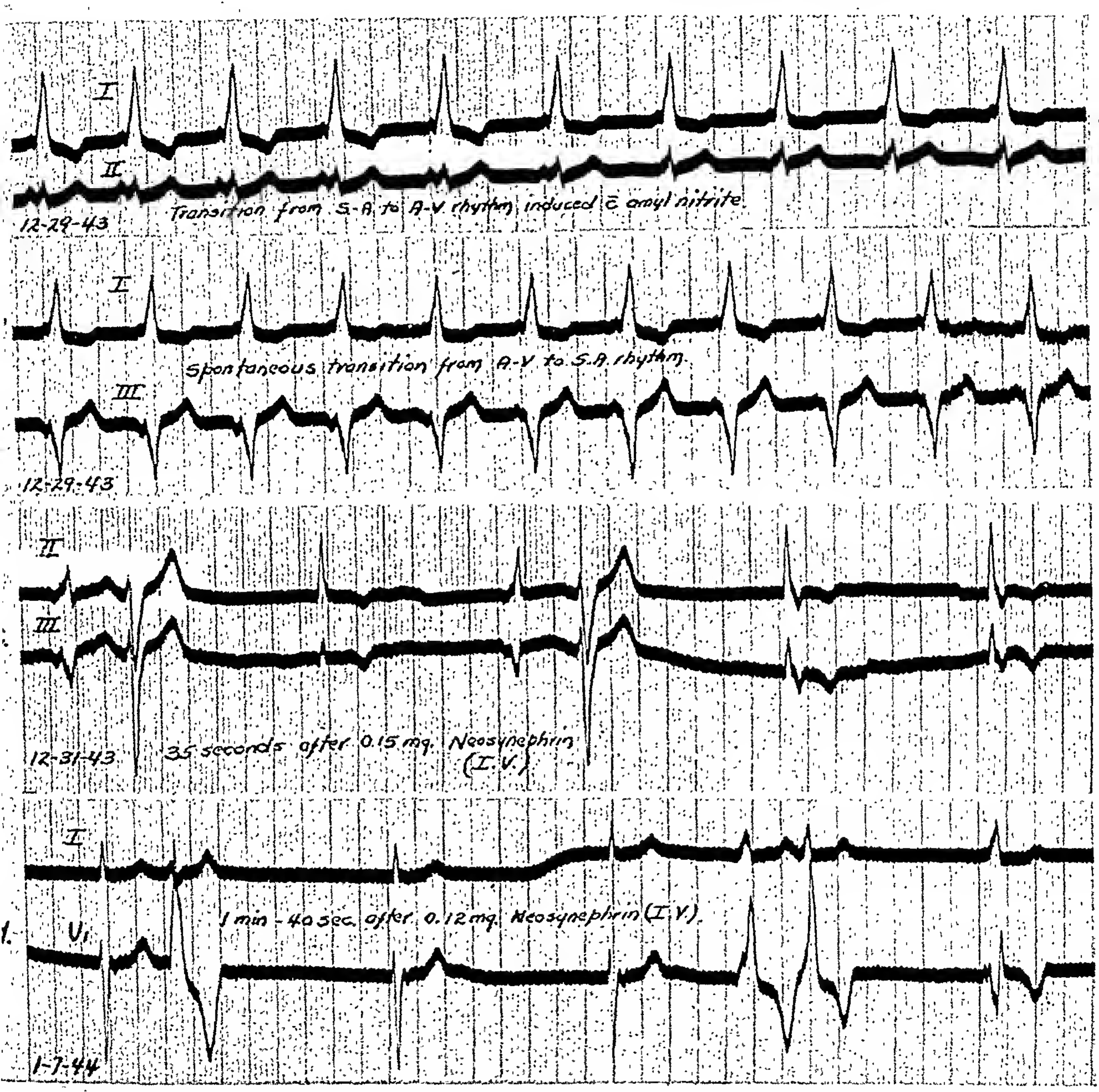

Fig. 15.—Case 10. *a*, Transition from sinus to atrioventricular rhythm arising in the upper levels of the atrioventricular node. *b*, Transition from atrioventricular rhythm arising in the upper part of the atrioventricular node to sinus rhythm. *c*, Taken after neosynephrin. Complexes 6 and 7 represent beats arising in the lower levels of the atrioventricular node; QRS is followed by an inverted P wave. Complex 3 is of the same type except that no P wave is visible. Complex 1 represents a beat arising in the higher levels of the atrioventricular node; the ventricular complex is anomalous. Complex 4 is transitional in form between Complex 1 and Complexes 3, 6, and 7. The remaining beats are ventricular extrasystoles. *d*, Complexes 1, 3, and 4 represent beats arising in the lower levels of the atrioventricular node; in the precordial lead (V_1), QRS is followed by an inverted P wave. Complexes 2, 5, and 6 represent ventricular extrasystoles. Complex 7 in V_1 resembles beats of questionable origin (see text), except that the QRS complex is triphasic instead of consisting of a broad, notched R. Note that the ventricular complexes of the atrioventricular beats are of the normal form.

7, 1944, either when the auricular rhythm was normal or when it was ectopic (compare Fig. 18 with Fig. 17). Whether these apparently spontaneous changes in the form of the ventricular complex were produced by variations in the order of ventricular activation or by variations in the position of the heart or in the placement of the exploring electrode is uncertain. Since they have no important bearing upon the problems under consideration, we call attention to their occurrence without further comment.

It will be noted that in every instance the effect of the onset of atrioventricular rhythm upon the QRS complexes of the leads in question was to make them more like those characteristic of Group A and less like those characteristic of Group B. When the QRS complexes of the sinus rhythm were represented by broad QS deflections in leads from the margins of the sternum or in Lead V_E, they acquired a conspicuous final R deflection when the pacemaker shifted to the atrioventricular node (Fig. 17). In Lead V_2, a QRS group of the rS form became a broad, notched R wave when atrioventricular rhythm developed (Fig. 17). In the records of Fig. 18 (Leads V_E, V_1, and V_2) the change is in the same direction, although here it is more the magnitude than the character of the components that is altered. Transitions recorded at a faster camera speed are reproduced in Fig. 19. These records are particularly interesting because they demonstrate beyond question (1) that the changes under consideration involved the form of the premature component of QRS; and (2) that when the pacemaker shifted the QRS complex did not acquire its new shape abruptly, for complexes intermediate in form between those characteristic of the sinus rhythm and those characteristic of the atrioventricular rhythm are clearly depicted.

On one occasion, abrupt, but otherwise similar, changes in the contour of the QRS complex were observed while sinus rhythm was continuously present. On Jan. 7, 1944, quinidine sulfate (0.47 Gm.) was given intravenously at 12:10 P.M. During the next thirty minutes the limb leads showed a pronounced arrhythmia, an increase in heart rate, and some modification of the ventricular complexes. Changes in the location of the pacemaker were frequent, and these produced effects comparable to those already described. No changes in auricular rhythm were recorded in the chest leads taken during this period. At 12:40 P.M., however, a record of Lead V_1, taken simultaneously with Lead III, showed changes in the character of the ventricular complexes, even though sinus rhythm was continuously present (Fig. 18). At the beginning of this record the QRS group of the chest lead consists of a broad, notched R, but from time to time two or three QRS complexes in succession are represented by broad downward deflections, followed by a small R component. In later parts of the tracing the number of complexes of the second type rapidly increases, and those of the first type disappear.

On Dec. 31, 1943, and on Jan. 7, 1944, records were taken after the intravenous injection of neosynephrin (0.15 mg. on the first date and

the leads from the seventh dorsal spine and from the right paravertebral and right scapular line at the level of this spine, the QRS group is represented by a QS deflection of small voltage. Transitions from sinus to atrioventricular rhythm, or the reverse, are shown in Figs. 15, 16, 17, 18,

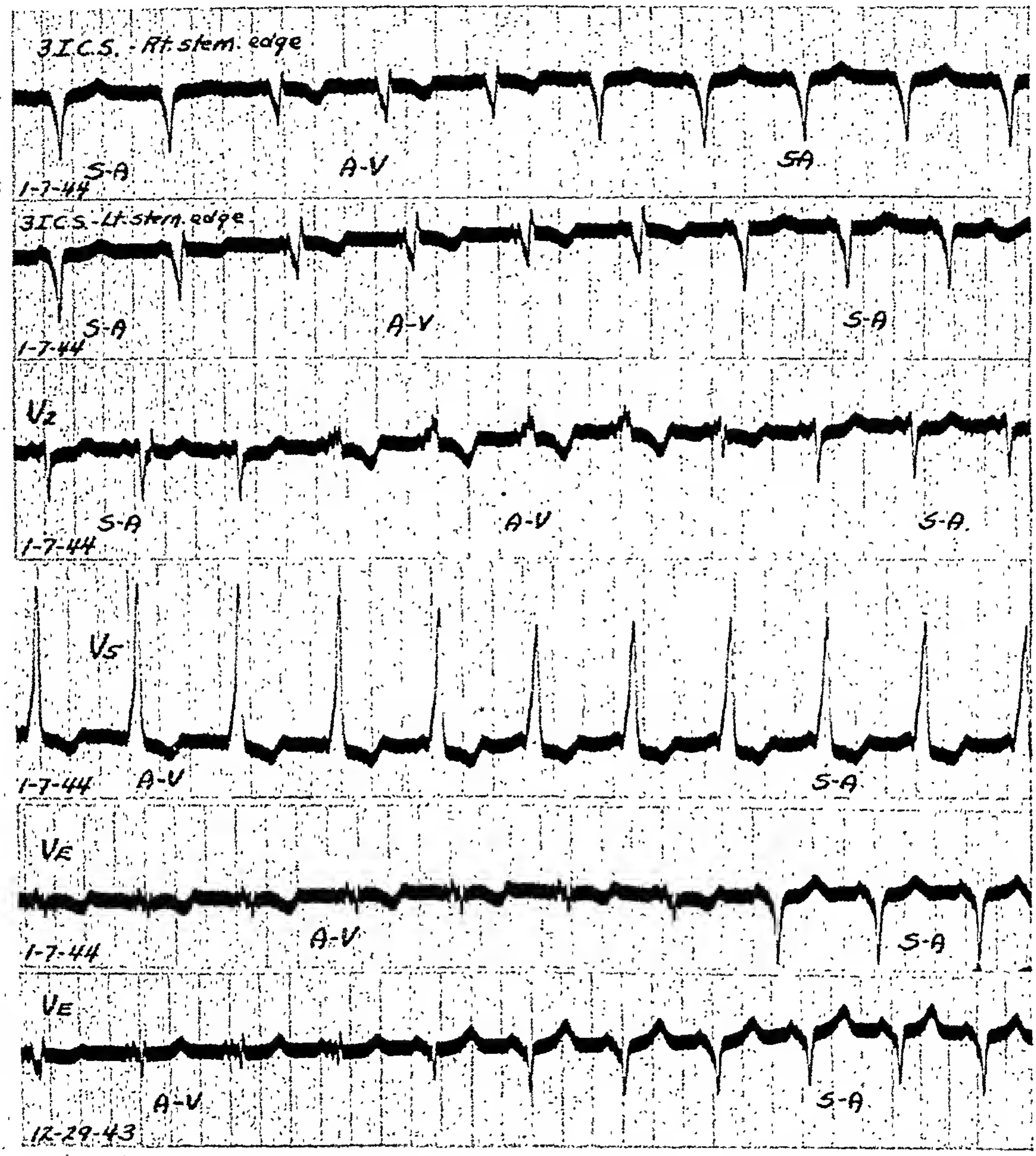

Fig. 17.—Case 10. Transitions from sinus rhythm to atrioventricular rhythm arising in the upper levels of the atrioventricular node, or vice versa. Precordial leads taken on Jan. 7, 1944.

and 19. In the limb leads (Fig. 15, *a* and *b*) the development of the ectopic rhythm was accompanied by a slight reduction in the voltage of the chief QRS deflection in Leads I and III; in the leads from the auricular levels of the esophagus it produced no noticeable change in the form of the QRS complex (Fig. 16). In Leads V_E, V_1, and V_2 (Figs. 17 and 18), however, its effect upon the character of the ventricular deflections was pronounced. It will be noted that the ventricular complexes of these leads varied in form independently of the location of the pacemaker; they were not of the same form on Jan. 11, 1944, as on Jan.

beats are immediately followed by inverted P waves both in Lead II and Lead III. In other instances the initial QRS component is preceded by a conspicuous dip, which apparently represents the first limb of an inverted P wave which is partly superimposed upon the ventricular deflections. In still others no trace of a P deflection is visible. There is also one ventricular complex which is intermediate in form between those that represent anomalous, and those that represent normal, atrioventricular excitation (fourth complex, Fig. 15, *c*). The later sections of the record show short runs of extrasystoles represented by ventricular complexes of variable form, followed presently by the return of the original cardiac mechanism. On the second occasion, similar, but somewhat more complicated, changes in the cardiac mechanism followed the injection of the drug. Most of the records show Lead I and Lead V_1, taken simultaneously, but there is also a tracing of a lead from the auricular level of the esophagus, taken simultaneously with Lead V_F. At the beginning, sinus rhythm is present and the QRS complex of Lead V_1 is represented by a broad QS deflection. Some seconds later the pacemaker shifts to the upper levels of the atrioventricular node, and this complex displays a broad Q followed by a small R wave. Then extrasystoles begin to occur, and there are frequent transitions from atrioventricular rhythm to sinus rhythm and back again (Fig. 16, *a* and *c*). Presently we come to a strip of record in which two or more beats in succession are represented by ventricular complexes of the normal form, *not* accompanied by visible P waves. In this same strip of record there are beats which are similarly spaced, but represented by ventricular complexes of still another form. In Lead V_1 the QRS group consists of a broad, deeply notched R; the first peak of this deflection is less than half as high as the second. In Lead I the QRS complex is like that of the beats of sinus origin, but of smaller voltage, and no P wave can be made out. It may be that these beats were of ventricular origin, for, in parts of the record, they are irregularly spaced and occur in rapid succession. In other sections of the record there are beats represented by normal ventricular complexes which display, in Lead V_1, an inverted P wave immediately following the QRS complex (first, third, and fourth complexes, Fig. 15, *d*). Beats of similar origin were recorded in a lead from the auricular level of the esophagus (Fig. 16, *b* and *d*).

These observations demonstrate that the His bundle and its branches were capable of functioning, and that impulses arising in the lower levels of the atrioventricular node spread to the auricles and to the ventricles in the normal manner.

Do the observed effects of atrioventricular rhythm upon the form of the ventricular complex support our working hypothesis or are they in conflict with it? Let us examine certain implications of this hypothesis which we have not had occasion to consider heretofore. If an accessory atrioventricular bundle is present, the excitatory process may

0.12 mg. on the second). On the first occasion standard limb leads were employed. Before the drug was given, atrioventricular rhythm of the kind already described was present. The earliest effects of the drug were slowing of the heart rate, variations in the location of the pacemaker, and arrhythmia due to ventricular extrasystoles. There are

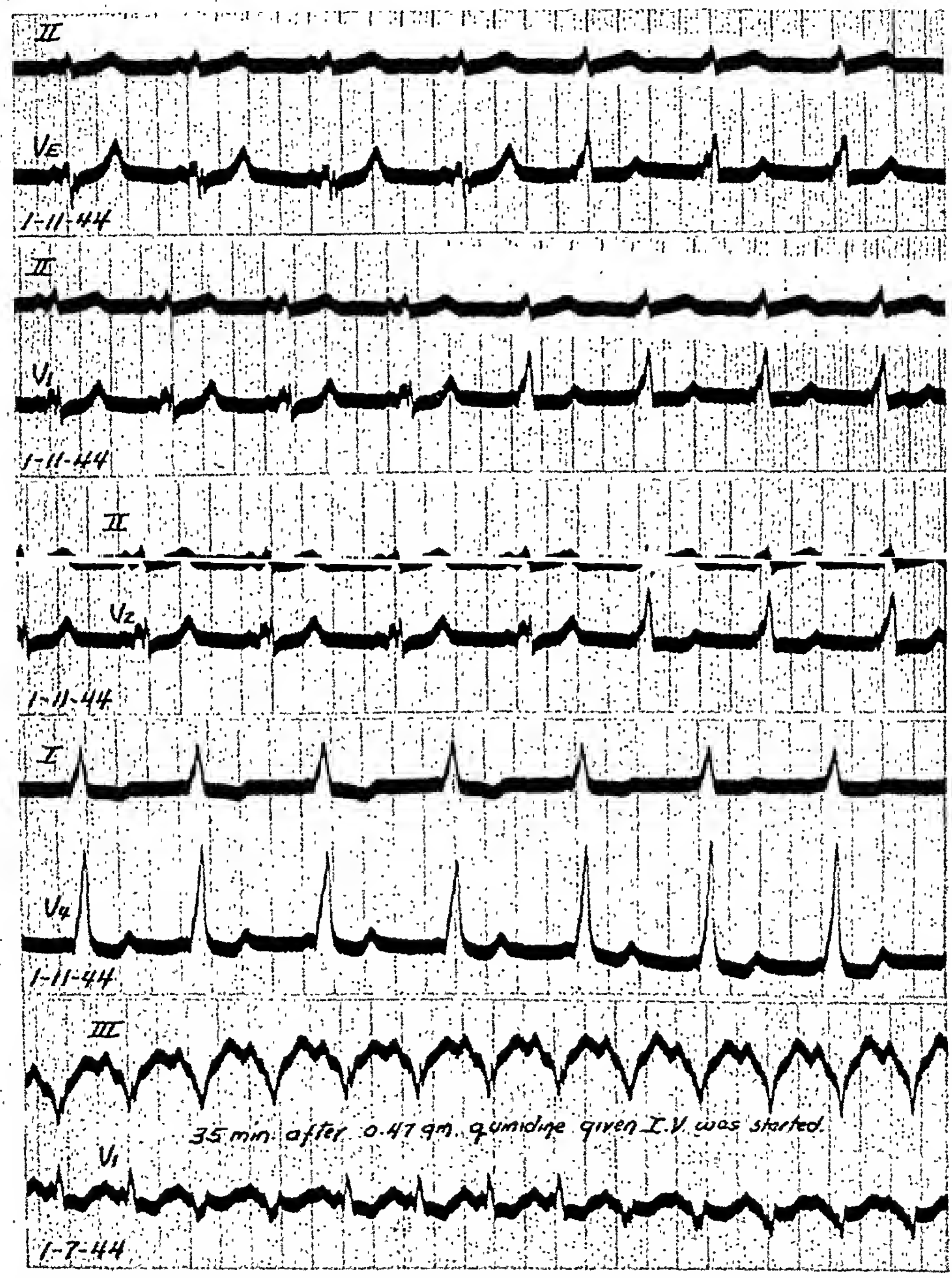

Fig. 18.—Case 10. *a*, *b*, *c*, and *d*, Transitions from sinus rhythm to atrioventricular rhythm arising in the upper levels of the atrioventricular node. Precordial leads taken simultaneously with a standard limb lead on Jan. 11, 1944. *e*, Variations in the form of the ventricular complex after the intravenous administration of quinidine when sinus rhythm was continuously present (Jan. 7, 1944).

short strips of record in which all of the beats, and others in which all of the beats other than those which are obviously ventricular extrasystoles, are represented by ventricular complexes of the normal form (Fig. 15, *c*). In the majority of instances the QRS deflections of these

spread to the ventricle both by the anomalous and by the normal route. Under these circumstances the place or places where ventricular excitation begins, and hence the form of the ventricular complex, will be determined by two factors: (1) the order in which the auricular ends of the two atrioventricular bridges pass into the excited state, and (2) the transmission times of the two atrioventricular bridges, and particularly the ratio of the transmission time of one to that of the other. The brevity of the P-R interval and the form of the ventricular complex in anomalous atrioventricular excitation requires us to suppose that the transmission time of the anomalous, is much shorter than that of the normal, pathway. In that case variations in the conductivity of either or both of the atrioventricular connections will not, unless they are very pronounced, prevent premature activation of the ventricles by the anomalous route, and will not, therefore, alter the form of the earlier fractions of the premature component of QRS. They will, however, change the relative magnitude of the anomalous and the normal components of this complex. In this connection we may mention the work of Fox, Travell, and Molofsky,[14] who showed that the administration of digitalis in a case of anomalous atrioventricular excitation may be followed by a pronounced increase in the duration of the QRS deflections, and that this effect is abolished by atropine. They attributed the alterations in the QRS brought about by these drugs to their well-known effects upon the conductivity of the atrioventricular node. We have examined the reproductions of their tracings and are not able to say with certainty that the form of the earlier fractions of the premature component either did or did not change in their experiments.

It is clear that the location of the pacemaker, by its effect upon the order of auricular activation, may determine which of the two pathways the impulse reaches first, and consequently influence the form of the ventricular complex in the same way and to the same extent as minor variations in their transmission times. Let us now assume that there are two accessory pathways, with approximately equal transmission times much shorter than that of the normal atrioventricular node and bundle. Under these conditions both the relative conductivity of these pathways and the location of the pacemaker will exert a profound influence upon the contour of the QRS complex as a whole, and also upon the form of its premature component by determining when and where ventricular excitation begins. Since active muscle is refractory to excitation, it may even happen that the excitation wave transmitted by one bundle will prevent the arrival of that transmitted by the other.

It seems to us, then, that our observations are not in conflict with the hypothesis that anomalous atrioventricular excitation depends upon the existence of one or more accessory atrioventricular bundles, if all of the implications of this hypothesis are carefully considered. We may suppose that, in Case 10, two bundles of this kind were present; that the changes in the form of the ventricular complex which accompanied the

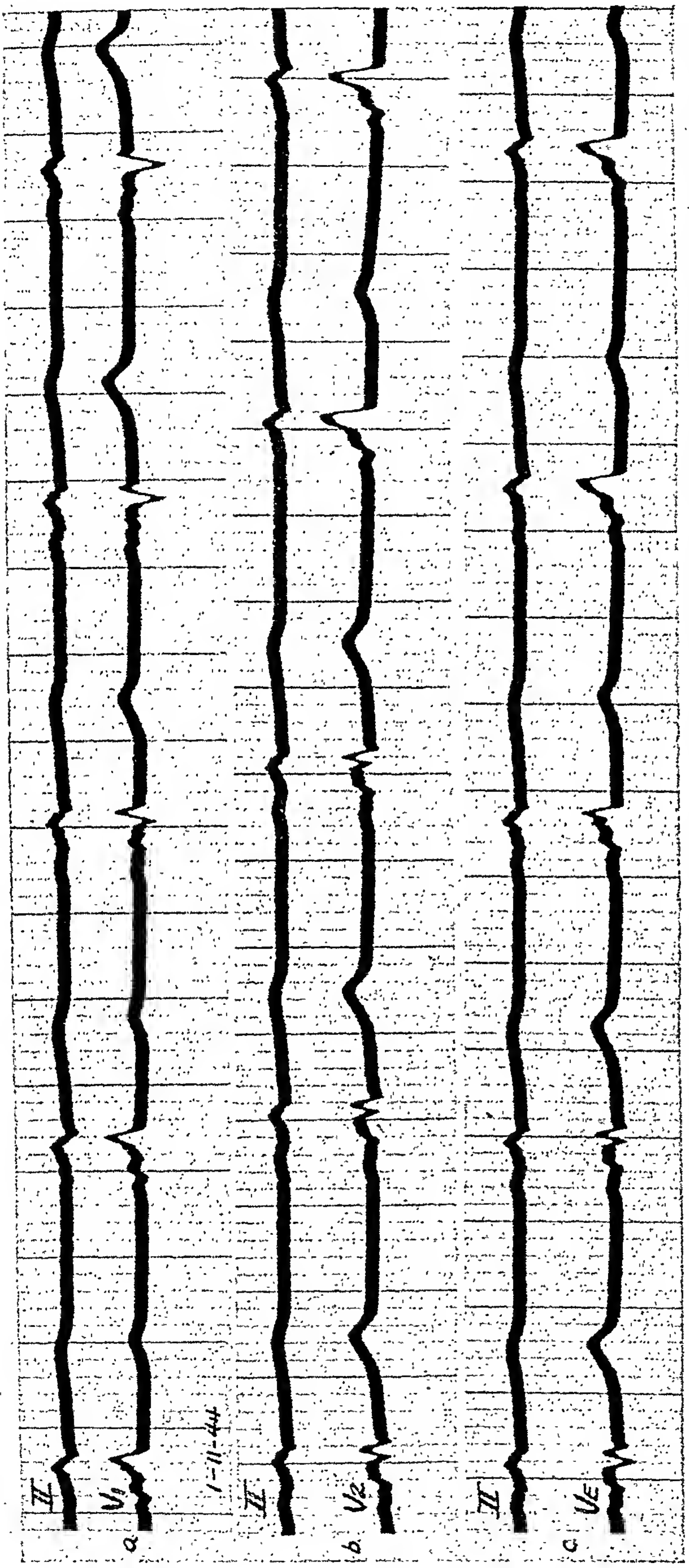

Fig. 19.—Case 10. Transitions from atrioventricular rhythm arising in the upper levels of the atrioventricular node (*a*), or vice versa (*b* and *c*), taken with the camera running at a speed of 75 mm. per second. Precordial leads taken simultaneously with Lead II. Note the transitional form of the third complex in *a* and of the corresponding complex in *c*.

unlikely that this played a part in determining the differences dependent upon the location of the pacemaker in Case 10. If these inferences are justifiable we must suppose that, in the cases of Group A, the ventricular end of the hypothetical accessory bundle was not in precisely the same location as in the cases of Group B, and, finally, that, in Case 10, there were two accessory bundles, one similar to that present in the cases of the first group and one similar to that present in the second.

PAROXYSMAL TACHYCARDIA IN ANOMALOUS ATRIOVENTRICULAR EXCITATION

Of the various types of paroxysmal rapid heart action that have been observed in cases of anomalous atrioventricular excitation, simple paroxysmal tachycardia of supraventricular origin is by far the most common. Its actual frequency is difficult to estimate, because relatively few cases of anomalous excitation in which cardiac symptoms are lacking are discovered.

Many years ago, Mines[16] produced circus contraction in rings of muscle cut from reptilian hearts in such a way as to include auricular and ventricular tissue and two atrioventricular junctions. The circulating excitation waves set up in these rings spread through the auricular and ventricular segments in succession, crossing one junction in the normal, and the other in the opposite, direction. It was suggested by the experimenter that paroxysmal tachycardia in man might be due to a similar mechanism.

The hypothesis that anomalous atrioventricular excitation is due to the presence of an accessory atrioventricular bundle has revived interest in Mines' conception of the nature of paroxysmal tachycardia. The hypothetical anomalous, and the normal, atrioventricular bundle provide the two atrioventricular junctions present in his experiments, and it has been postulated that, under proper conditions, an impulse might pass from the auricles to the ventricles by way of the atrioventricular node and bundle, and, by returning to the auricles via the anomalous bridge, initiate circus contraction. This is a plausible hypothesis, but as yet no direct evidence pointing to the existence of the postulated mechanism in an observed attack of paroxysmal tachycardia has appeared. We shall, therefore, call attention to some peculiarities of the paroxysms recorded in one of the cases of our series.

In some of the electrocardiograms taken in Case 7 there are extrasystoles represented by QRS complexes of normal outline which are immediately followed in Lead I by an inverted, and in Lead III by an upright, P wave (Fig. 20, *c*). The paroxysms of tachycardia appear to be made up of a rapid succession of beats of this type (Fig. 20, *c* and *d*). On two occasions the onset of a paroxysm was recorded (Fig. 20, *a* and *b*). In both instances the complexes of the beats of sinus origin which immediately precede the ectopic rhythm are of the anomalous type. The first ectopic beat is represented by ventricular deflections of more

onset of atrioventricular rhythm in this case were due to the effect of the order of auricular activation upon the time when excitation of the auricular end of each of these bundles began; and that the changes in the form of the ventricular complex which occurred independently of changes in the location of the pacemaker after the administration of quinidine were dependent upon unequal changes in the transmission times of the two pathways brought about by this drug.

It is possible that the changes in the ventricular complex that accompanied the onset of atrioventricular rhythm may be satisfactorily accounted for in another way. It is known that transitions from sinus rhythm to atrioventricular rhythm are sometimes accompanied by alterations in the ventricular complex even when the ventricles are activated in the normal manner. As far as we know, such changes are ordinarily of very small magnitude, and have been described only in connection with ectopic rhythms arising in the lower levels of the atrioventricular node. An isolated instance in which the onset of a rhythm of this sort was associated with very striking modifications of the ventricular deflections in standard limb leads has, however, been reported.[2] This phenomenon is apparently due to imperfect distribution of the excitation process to all of the fibers of the His bundle. The occurrence of reciprocal rhythm in association with a low atrioventricular pacemaker is further evidence that cross conduction in the His bundle may be limited, and that this structure and the atrioventricular node do not always function as a single, uncomplicated channel for the transmission of impulses. Nevertheless, we doubt very much whether faulty cross conduction in the His bundle played an important role in the production of the phenomenon under consideration. In the first place, it is difficult to understand why the His bundle and its subdivisions should conduct normally when the ectopic center was on the ventricular side of the junctional tissues, and abnormally when this center was in the upper part of the atrioventricular node.

The other evidence bearing upon this problem is of an indirect kind. We have pointed out that the differences between the anomalous ventricular complexes associated with the more common of the two atrioventricular rhythms observed, and those that represent responses to the sinus node are similar in character to the differences between the ventricles complexes recorded in the cases of Group A and those recorded in the cases of Group B. In both instances these differences were pronounced in the leads from the right side of the precordium, and slight in the leads from the left side of the precordium and from the auricular levels of the esophagus. It is evident that, in Case 10, they were dependent upon differences in the order of ventricular activation. We infer that the differences between Group A and Group B had a similar origin. On the other hand, there is no reason to suspect that the differences between these two groups of cases were in any way dependent upon faulty cross-conduction in the His bundle, and, consequently, it seems

node. The unusual character of the P waves led us to consider another possibility. Suppose that the path through the atrioventricular node was blocked when the ectopic impulse was liberated, and that the peculiar P waves represent auricular excitation by impulses conducted from the ventricles to the auricles via the anomalous bundle. In that case the excitatory process could return to the ventricle by the normal route, and thus initiate a paroxysm. It has been pointed out that, at the beginning of a paroxysm, there was evidence of aberrant intraventricular conduction. To explain this we may postulate that the junctional or ventricular tissues had not, as a rule, recovered completely at the time when the ectopic impulse was liberated. As a result, many extrasystoles, followed by retrograde stimulation of the auricles via the anomalous path, failed to initiate a paroxysm, and, when a paroxysm was initiated, there was aberrant conduction until the refractory period of these tissues shortened in response to the reduction in cycle length. Even during some of the longer paroxysms there was alternation of the form of the ventricular complex, indicating that intraventricular conductivity was depressed (Fig. 20, *d*). It should also be mentioned that in many instances the ventricular complexes of the single extrasystoles were not accompanied by P waves, indicating that retrograde stimulation of the auricles often failed.

We record these observations not because we consider them important evidence bearing on the problem at issue, but in the hope that those to whom the opportunity may come will make a careful study of the mechanism of the paroxysms of tachycardia that occur in cases of anomalous atrioventricular excitation from the point of view expressed. We frankly admit that the suggested interpretation of them is highly speculative, and that it does not explain the unusual P waves upon which it is based much more satisfactorily than the more conventional one.

FURTHER DISCUSSION AND CONCLUSIONS

Since anomalous atrioventricular excitation is a rare and relatively innocuous condition, it is not of major importance from the purely clinical standpoint. We do not, however, believe that this anomaly should be completely ignored by military and insurance examiners as without bearing upon the health or life expectancy of those who exhibit it. The paroxysms of tachycardia to which such persons are predisposed may certainly lead to death, and there is no reason to suppose that they may not also give rise on occasion to sudden giddiness, faintness, or syncope. In the pilot of an airplane, symptoms of this kind could result in disaster. Nor does the lack of a history of such paroxysms in the past necessarily mean that they will not occur in the future. It would seem wise, therefore, to look upon this condition as always involving such hazards as attacks of extremely rapid heart action entail.

The importance of this disorder and the interest it has aroused among cardiologists depend, however, not upon its clinical implications, but

normal outline, but the ventricular complexes of the first few paroxysmal beats differ considerably in form from those that follow them. The differences are of the kind usually attributed to aberrant intraventricular conduction. Since the first QRS complex of the abnormal rhythm is not preceded by a P wave, the ectopic rhythm must be ascribed to impulses arising in the lower levels of the junctional tissues. It is possible that the impulses responsible for the paroxysmal beats, as well as those that

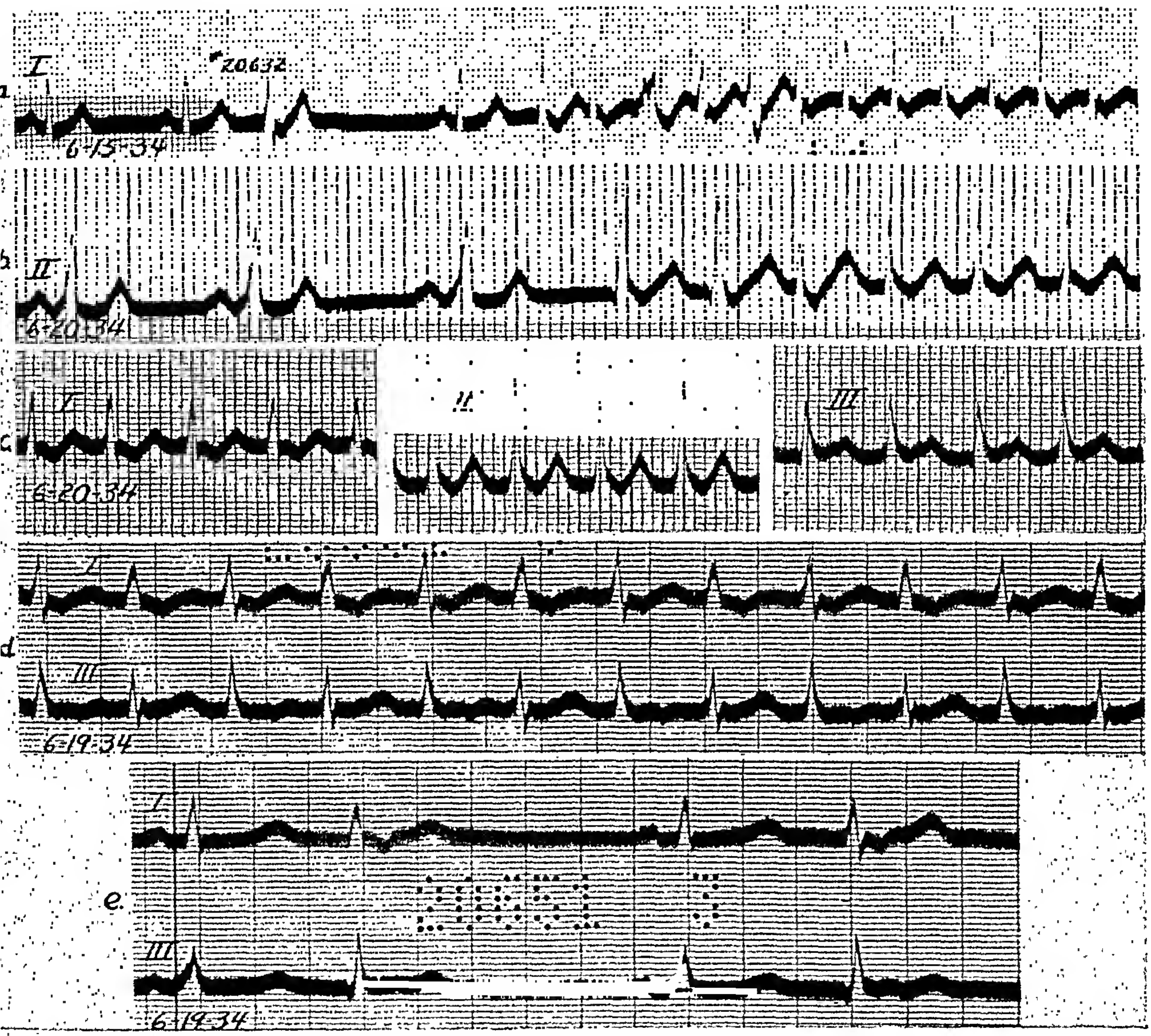

Fig. 20.—Case 7. *a* and *b*, Onset of paroxysmal tachycardia on two different occasions. *c*, Paroxysmal tachycardia on June 20, 1934; note negative P waves in Lead I and upright P waves in Lead III. *d*, Paroxysmal tachycardia on June 19, 1934. There is alternation of two types of ventricular complexes; compare with *e*, in which similar types of ventricular complexes represent extrasystoles of atrioventricular origin.

provoked the single extrasystoles, reached the auricles by the same route as in ordinary atrioventricular rhythm. The sole objection to this supposition is that it does not explain why the P waves are inverted in Lead I and upright in Lead III, and not the reverse, as is almost always, if not invariably, the case when the auricles are activated by the retrograde transmission of an impulse through the atrioventricular

rived from the invaginated atrial canal was observed by Mall in human embryos.

It is logical to suppose, then, that any accessory bundle in the human heart must represent some remnant of the invaginated auricular canal. One difficulty with this supposition is that the electrocardiograms of fish, amphibians, and reptiles, and of the chick embryo display a conspicuous P-R interval[21] which, in comparison with the other intervals of the curve, is not very different from that of the normal human electrocardiogram. Why, then, should an accessory bundle derived from the invaginated auricular canal conduct the cardiac impulse with much greater speed than the normal atrioventricular bridge? Eckey and Schäfer[22] have ascribed the anomalous component of QRS in cases of the Wolff-Parkinson-White syndrome to the action currents of remnants of the original atrioventricular funnel persisting in the fully developed heart. Without considering other objections to this hypothesis, we may point out that the component in question seems much too large to be accounted for in this way.

Of the various hypotheses that have attributed anomalous atrioventricular excitation to a physiologic, rather than a structural, anomaly, the one that deserves most serious consideration is that which ascribes this disorder to the direct stimulation of ventricular fibers by the action currents of adjacent auricular muscle. Attempts to excite the ventricles to contraction in this way in experiments on animals have thus far failed, but if it should be proved possible, an anomaly of this kind would account as well as a hypothetical accessory muscular bridge for all of the phenomena observed. It should be noted, however, that observations pointing clearly to the presence of partial block in the accessory pathway would greatly strengthen the view that the anomaly is structural.

In our opinion, there has not yet been advanced any tenable hypothesis which ascribes electrocardiograms of the kind under consideration to anomalies that involve no part of the heart other than the normal junctional tissues. To be satisfactory, any hypothesis of this sort must explain the following observations relating to electrocardiograms of this type: (1) the QRS complex seems to be made up of a normal component, which begins at the normal time, and an anomalous component which begins several hundredths of a second earlier; (2) the precordial electrocardiogram is very different from the precordial electrocardiograms obtained in bundle branch block, complete or incomplete, right or left; (3) the form of the ventricular complex, including that of the premature component of QRS, is sometimes determined by the order of auricular excitation; (4) when two pacemakers, one in the sinus node and one in the upper levels of the atrioventricular node, are sending out impulses almost simultaneously, QRS complexes transitional in form between those characteristic of the sinus rhythm and those characteristic of the atrioventricular rhythm may occur. This observation implies that in one and the same cycle two supraventricular impulses may reach

upon its bearing on our conceptions of the mechanisms responsible for the normal sequence of auricular and ventricular contraction and the interval which separates them. We must ask ourselves whether it is possible to explain satisfactorily the electrocardiographic anomalies which characterize it without revising ideas concerning these mechanisms that seem to rest upon a solid experimental foundation. We refer particularly to the belief that in the normal mammalian heart the cardiac impulse is transmitted to the ventricles by the successive activation of the components of a specialized muscular or neuromuscular pathway, consisting of the atrioventricular node, the His bundle, and the subdivisions thereof. There is abundant experimental evidence that section of this bundle or of both its right and left branches produces complete atrioventricular dissociation. The action currents of these structures and of the node have, however, never been recorded, and there is no direct evidence available as to exactly what happens to the cardiac impulse in the latter.

We must suppose that the electrocardiographic peculiarities encountered in the syndrome under consideration depend upon an anatomic or a functional anomaly. Unless we abandon our present conceptions, any anomaly of the first sort must involve either (1) the existence of one or more muscular or neuromuscular accessory bridges extending from the auricular to the ventricular myocardium, or (2) some structural peculiarity of the atrioventricular node, bundle, or bundle branches. These two possibilities are not completely distinct, for it matters little whether the accessory channel for the transmission of impulses is widely separated from, or lies within, the same sheath as its fellow. With reference to the manner in which an accessory bundle might arise in the course of the heart's development, we may refer to observations on the junctional tissues of the embryonic mammalian heart and of the mature heart in lower orders of animals made by Keith and Flack,[17] Keith and Mackenzie,[18] Mackenzie,[19] and Mall.[20]

According to these authors, the mammalian atrioventricular bundle is derived from the invaginated portion of the auricular canal. Portions of this funnel atrophy as the lateral endocardial cushions, which form the parietal auriculoventricular valves, develop. In some fish the ring is interrupted at two points, so that the funnel is replaced by two strands. When the single ventricle of the lower forms is divided into two chambers, that part of the funnel which lies on the left side entirely disappears, so that the connection between auricular and ventricular muscle is present only on the right side. This reduction continues until, in the mammal, only the His bundle remains. In the monotreme echidna there is, in addition to an atrioventricular bundle similar to that of mammals, another leash of tissue which descends to the ventricles in the posterior angle between the parietal and septal valves on the right side. The sequence of changes by which the His bundle is de-

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ADDENDUM

The monograph of Richard F. Öhnell, entitled *Pre-Excitation, A Cardiac Abnormality*, Stockholm, 1944, P. A. Norstedt & Söner, was not available when this article was written. In one of Öhnell's cases careful histologic examination of the atrioventricular junction disclosed an accessory atrioventricular bundle about 6 mm. long which connected the myocardium of the left auricular wall with the subepicardial myocardium of the left ventricle. This bundle was dorsal to the mitral orifice and about 4 cm. from the ventricular septum. An accessory bundle of this sort could explain the occurrence of electrocardiograms of the kind obtained in cases which we have placed in Group A.

the ventricles without interfering one with the other; (5) when the pacemaker shifts to the lower levels of the junctional tissues, the ventricular complex assumes the normal form. This suggests that anomalous atrioventricular excitation is impossible when ventricular excitation occurs simultaneously with, or precedes, auricular. It seems to us that any hypothesis that can satisfactorily account for these phenomena must provide more than one distinct channel for the transmission of impulses from auricles to ventricles.

CONCLUSIONS

The form of the ventricular complex in unipolar leads from the esophagus, precordium, and other parts of the thorax suggests that, in anomalous atrioventricular excitation, the dorsal wall of the ventricles is activated prematurely by impulses of supraventricular origin. There is evidence also that the normal atrioventricular node and bundle continue to function in this condition.

There are two types of cases, which differ as regards the form of the ventricular deflections in leads from the right sternal margin and adjacent parts of the right side of the thorax. The differences between these two types of cases are due, at least in part, to differences in the order of ventricular activation.

The anomalous ventricular complex assumes the normal form when the pacemaker shifts to the lower levels of the junctional tissues.

In some cases the location of the auricular pacemaker determines the form of the premature component of the QRS group, as well as that of the anomalous ventricular complex as a whole.

Our observations support the view that, in this disorder, impulses pass from the auricles to the ventricles not only by way of the atrioventricular node and His bundle, but by one or more additional channels.

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The patient confirmed this history of employment. In his opinion, there was scarcely any visible dust about the crusher. Moreover, he worked at the other end of the building, upstairs, and did not operate this machine. His past history revealed that he had never been in the mines, and, as far as he knew, had never had an occupational exposure to dust. He had been under a physician's care for a sore throat for three or four days, seven years before. There had been no other illness, and no suggestion of rheumatic fever.

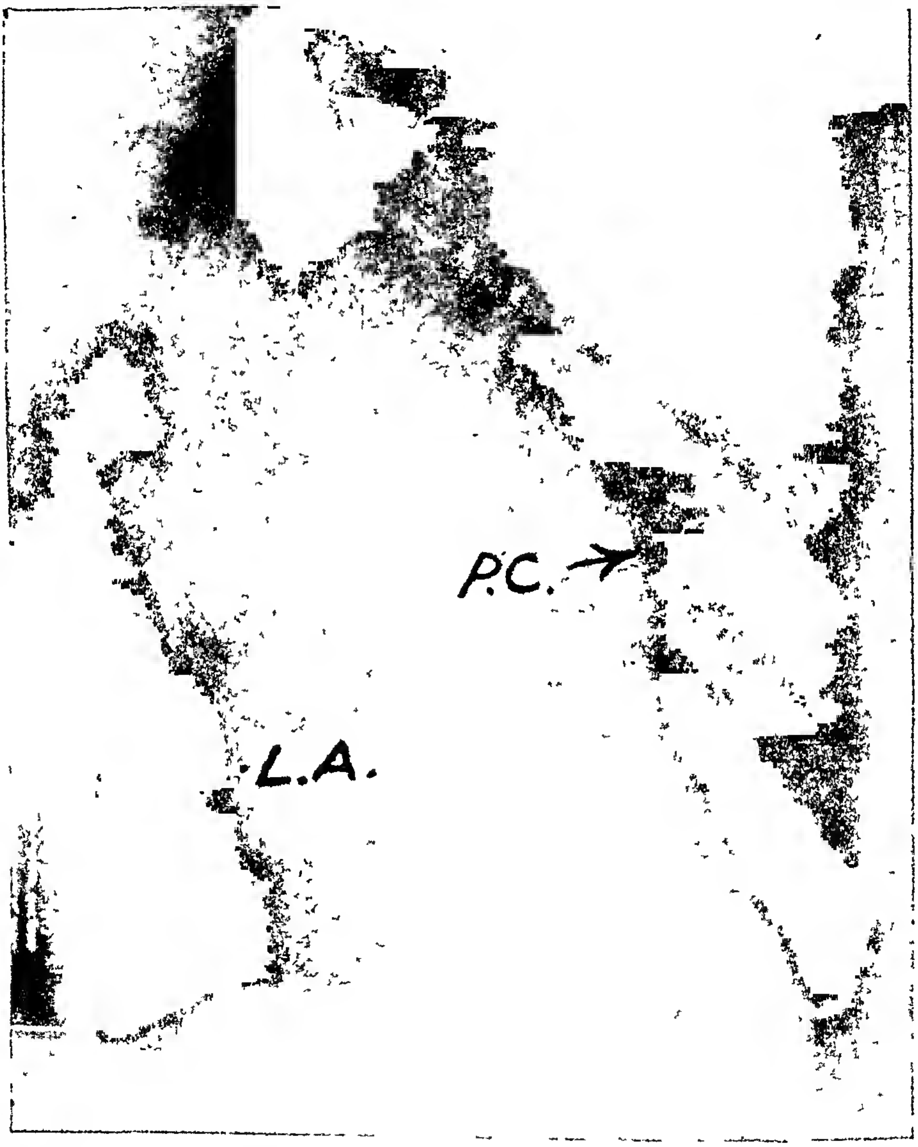

Fig. 1.—Right anterior oblique view of heart, showing prominence of the pulmonary conus (P.C.) and left atrium (L.A.).

The patient said that his usual weight was 145 pounds, dressed, and that there had been no recent change. His strength, endurance, and appetite were good. He had had no chest pain of any kind. Occasionally he had a slight cough which was productive of white sputum. In his opinion, the slight shortness of breath on exertion from which he suffered was due to lack of exercise.

PULMONARY ROENTGENOGRAPHIC CHANGES DUE TO MITRAL STENOSIS SIMULATING THOSE DUE TO SILICOSIS

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ROUTINE roentgenographic studies of the lungs of apparently normal persons have become increasingly widespread in recent years. Their use by the armed forces in performing screening examinations for prospective inductees is their most extensive application. Antedating this application, however, industry, with its developing awareness of the extent of the silicosis hazard, had discovered the value of periodic roentgenographic examination of the lungs of exposed men in detecting pulmonary changes due to silicosis before disability had occurred.

The value of these roentgenographic surveys is subject to certain restrictions. It has been emphasized repeatedly that a number of conditions other than silicosis cause miliary shadows in the lungs. The form and pattern of the shadows are often characteristic of a particular condition, but the definitive differential diagnosis can be made only on clinical grounds.[1, 2, 3] The following case is presented in order to emphasize the fact that the diagnosis of silicosis must be based on clinical evidence, not on roentgenographic changes alone.

CASE REPORT

The patient was a married white man, 26 years of age, who was referred to us because a diagnosis of silicosis had been made in July, 1943, by the medical examiners for the Construction Battalion of the Navy, and because the opinion had been expressed, after two subsequent roentgenologic examinations of his lungs, that the pulmonary changes were consistent with this diagnosis.

An employment survey made by Dunn and Bradstreet revealed that this man had had no hazardous dust exposure before he became a catalyst operator in April, 1943, for the company he was working for at the time of his examination in October, 1943.

By July, 1943, he had been working eighty-three days in a building in which a crusher of filter material was operated. This filter material consisted of finely ground silica, with a binder of potassium silicate. It was received in rather large pieces, which were then crushed to lumps about the size of a finger tip for use in the filters. The silica was not ground and the filter material was not prepared at this site; the only operation was the crushing. This was done in a crusher provided with exhaust ventilation, and "fines" were sifted out also under exhaust ventilation. The operation was not considered to be a dusty one. The major part of the patient's work, although carried out in the same building, was done at some distance from this crusher.

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Received for publication April 6, 1944.

The aortic second, pulmonic second, and second heart sound at the mitral area were widely split. The first sound at the mitral area was markedly accentuated; the pulmonic second sound was sharp and accentuated. There was a rumbling, holodiastolic bruit, with presystolic accentuation, at the apex. In the absence of aortic insufficiency, this bruit is pathognomonic of mitral stenosis. No other bruits were heard before or after exercise in any position. There was no gallop rhythm, thrill, or rub.

Fig. 3.—Anteroposterior view of chest, Sept. 7, 1943.

Examination of the abdomen revealed no tenderness and no masses. The liver was normal in size. The kidneys and spleen were not felt. There was no peripheral edema, no adenopathy, and no venous distention.

The urine was yellow and clear, with a specific gravity of 1.020; tests for albumin and sugar gave negative results. The centrifuged sediment showed mucus and occasional leucocytes. The hemoglobin content of the

Physical examination, Oct. 19, 1943, showed that the patient was a well-developed, well-nourished, slight, intelligent, cooperative, and cheerful young man who looked well. His height was 5 feet 7¾ inches; weight, 138 pounds, stripped; temperature, 98.9° F. (mouth); pulse rate, 66; respirations, 16; blood pressure, 130/75 (right arm, sitting); and vital capacity 2.95, 3.10, and 3.30 liters, standing. (The normal vital capacity for his height is 4.4 liters.)

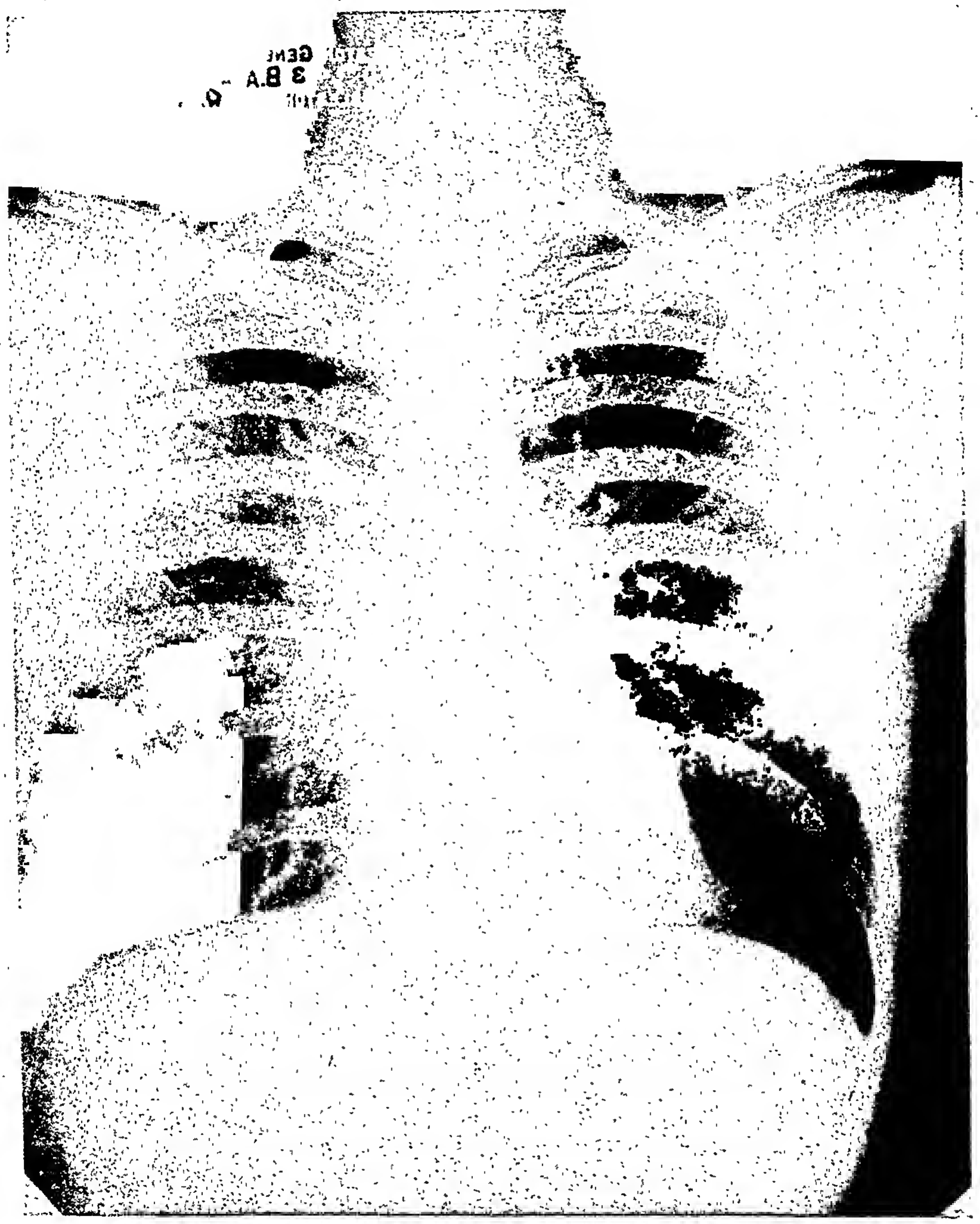

Fig. 2.—Anteroposterior view of chest, July 30, 1943.

The chest was symmetrical, with no increase in the anteroposterior diameter. The diaphragm moved well; the right side was little higher than the left. The lungs were normal anteriorly and posteriorly to percussion and auscultation. There were no changes in tactile or vocal fremitus.

The cardiac mechanism was normal. The posterior maximal cardiac impulse was in the fifth intercostal space in the left midclavicular line.

heaviest in the lung areas between the hila and lateral chest walls, although some mottling was present at the apices and bases. The mottling was regarded as infiltrative, and was not nearly dense enough to be the result of scarring or fibrosis. It was felt that many of these more or less discrete-looking lesions represented points at which small bronchi crossed each other (Figs. 2, 3, 4, and 5). The pleura and diaphragm appeared normal.

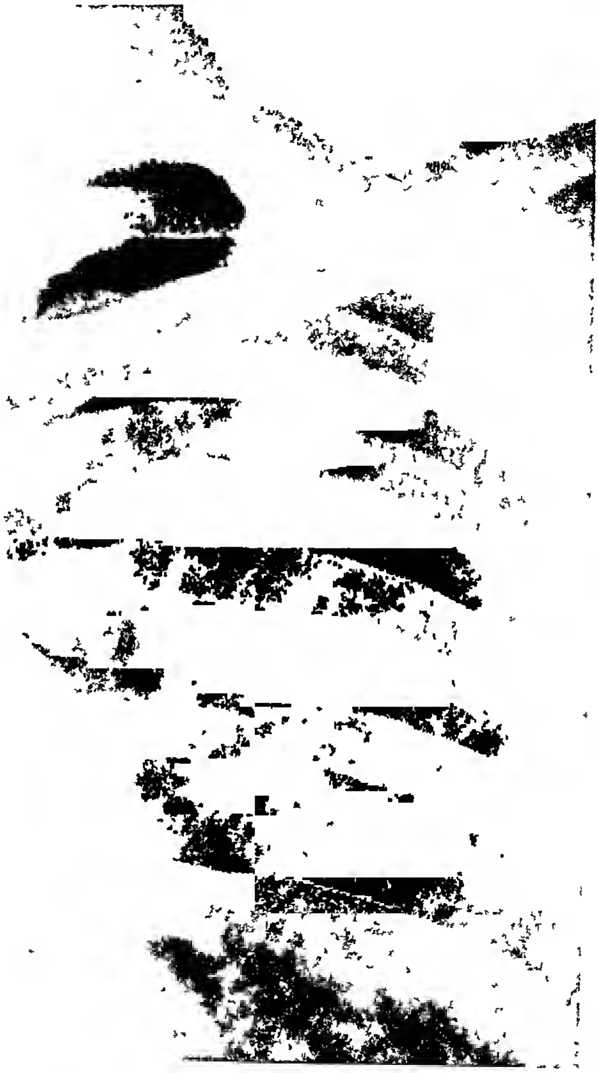

Fig. 5.—Detail of chest roentgenogram of Oct. 19, 1943, showing the soft mottling with the suggestion of nodulation. The nodulation is thickest near the hilum, and thins out toward the apex and the periphery of the lungs.

An electrocardiogram (Fig. 6) showed that the auricular and ventricular rates were 60, with slight sinus arrhythmia and sinus mechanism. The P-R interval was 0.17 second, and the QRS interval, 0.08 second. P_1 was prominent and notched, and P_2 and P_3 were prominent and slurred. There was no axis deviation. The S-T_2 and S-T_3 segments were elevated about 1 millimeter. T_2 and T_3 were upright and peaked.

The patient's employer reported that roentgenograms had been made on thirty-three of the employees who had been, and were still, working in the catalyst unit in which the patient was employed. The periods of exposure of these men varied from one to six months. In several

blood was 17 Gm. (Sahli); the erythrocytes numbered 5,040,000, and the leucocytes, 8,350, per cubic millimeter; of the latter, 73.5 per cent were polymorphonuclear leucocytes, 21 per cent were lymphocytes, 5 per cent were monocytes, and 0.5 per cent were basophiles.

The patient's mean diurnal oral temperature for the seven days preceding the examination, taken by the plant physician, was 97.5 ± 0.4° F.

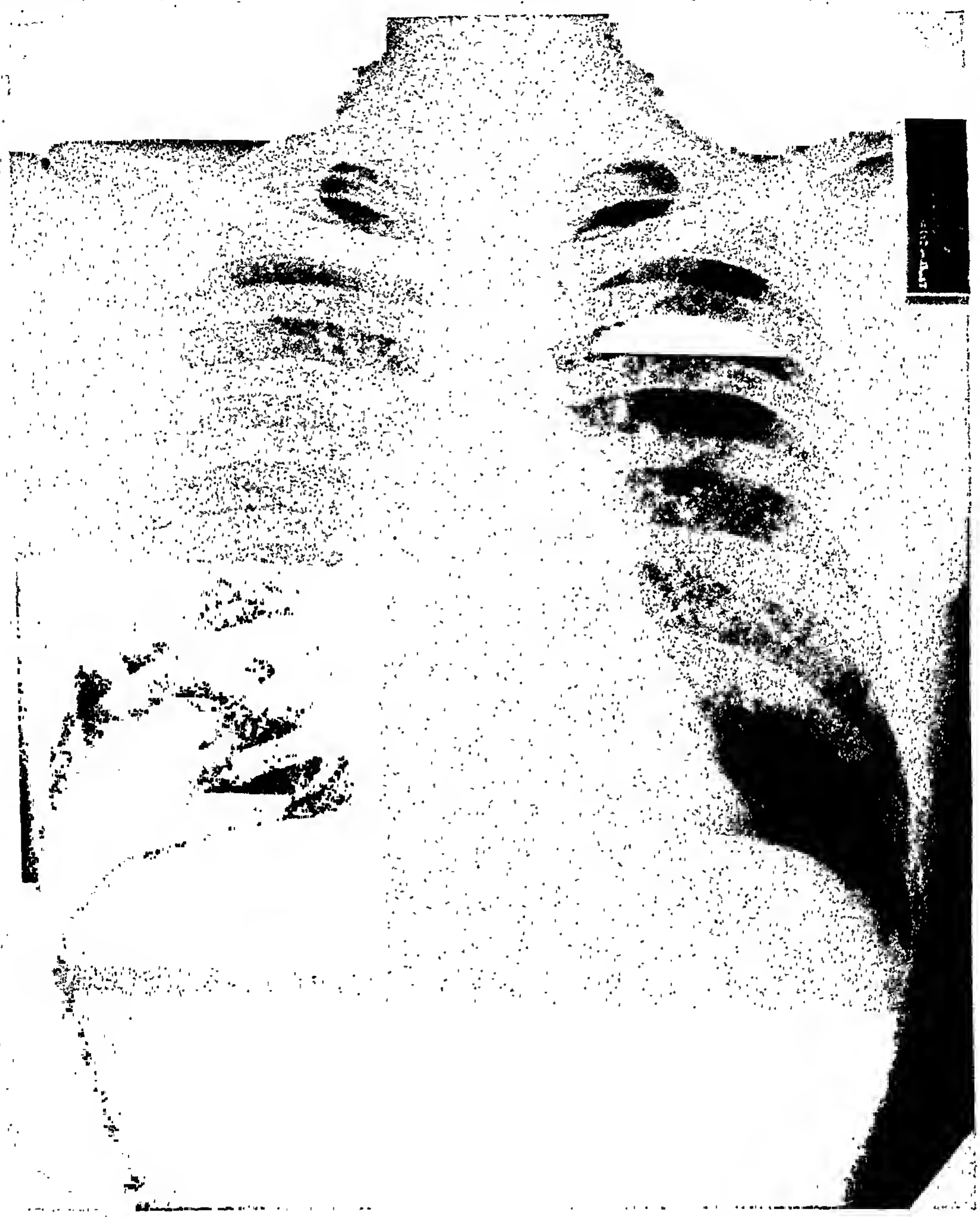

Fig. 4.—Anteroposterior view of chest, Oct. 19, 1943.

Teleostereoscopic roentgenographic examination of the chest by one of us (H. G. R.) showed that the retrosternal width was 5.5 centimeters. The greatest cardiac width was 14 cm., and the thoracic was 31.5 centimeters. The cardiac waist line was obliterated, and there were very slight accentuation of the pulmonic conus and definite accentuation of the left auricular outline. Fluoroscopic examination showed that the left auricle was definitely enlarged (Fig. 1). With barium in the esophagus, no gross displacement was noted. The heart action was normal. Throughout both lungs there was diffuse mottling. This was

both lungs a miliary appearance. This can be remarkably like the picture of pneumonoconiosis or miliary tuberculosis. Differentiation from these conditions is made possible, in his opinion, by the fact that, with mitral stenosis, the spots diminish toward the periphery. Attinger[5] reported that the usual pulmonary roentgenographic picture in mitral stenosis is a diffuse, even clouding in the lung bases, but that miliary lung stasis occurs occasionally, and can scarcely be distinguished from miliary tuberculosis. He stated that in miliary lung stasis the nodules are thickest in the central parts of the lungs, whereas the inferior portions, and particularly the apices, are clear. Anglin[6] reported a case of miliary stasis, with chronic passive congestion as a result of mitral stenosis, which simulated miliary tuberculosis. He stated that, although the character and distribution of the shadows suggest the correct diagnosis, they are not in themselves sufficient to distinguish between the two conditions. Roch[7] reported the case of a young woman who had been treated for tuberculosis for twelve years. There were shadows of vascular stasis in the hilar and basal regions, but the apices and costophrenic angles were clear. At autopsy she was found to have had, not tuberculosis, but mitral stenosis. Arif[8] reported the case of a miner who, after working for five years in an area where there was much silica dust, was found to have mitral stenosis, and roentgenograms of his lungs showed the finely nodular appearance of pneumonoconiosis. Arif stated that exposure in this case had been too brief to cause silicotic changes in the lungs. The patient was still alive at the time of his report.

In all these cases of mitral stenosis with roentgenographic miliary pulmonic shadows, there were symptoms of pulmonary disease, which was not true in the case here reported. Sosman[9] has noted considerable dilatation and congestion of the pulmonary vessels in cases of mitral stenosis, without any clinical signs or symptoms of illness.

OBSERVATIONS FROM THE LITERATURE ON THE OCCURRENCE OF SILICOSIS AND THE AMOUNT OF EXPOSURE REQUIRED TO PRODUCE IT

In examining a group of fifteen workmen exposed in three different occupations to high concentrations of silica dust, Gardner[10] noted that all but one had developed the histologic lesions of silicosis by the time of death. Whether the exposures were as short as eight to seventeen months could not be established with certainty. In the group as a whole, roentgenographic evidence of silicosis was very slight or absent. The only changes that could readily be recognized were due to infection, although the amount of silica in the lungs was measured, and was found to equal that present in the lungs of South African gold miners with silicosis who had been exposed to silica dust for long periods. Kilgore[11] reported a study of six men who had been exposed to alkaline silica mixtures. Symptoms developed within nine, eleven, fourteen, and twenty-four months, respectively, in four of the six men who worked

cases, particularly those of eight men feeding the crusher, the exposure was, in their opinion, much greater than that of the patient. Roentgenograms of these men were made and examined by a local radiologist, who, in all cases, reported nothing abnormal. We examined the roentgenograms of the eight who worked in the vicinity of the crusher and confirmed this interpretation. None of these men had developed symptoms suggestive of silicosis.

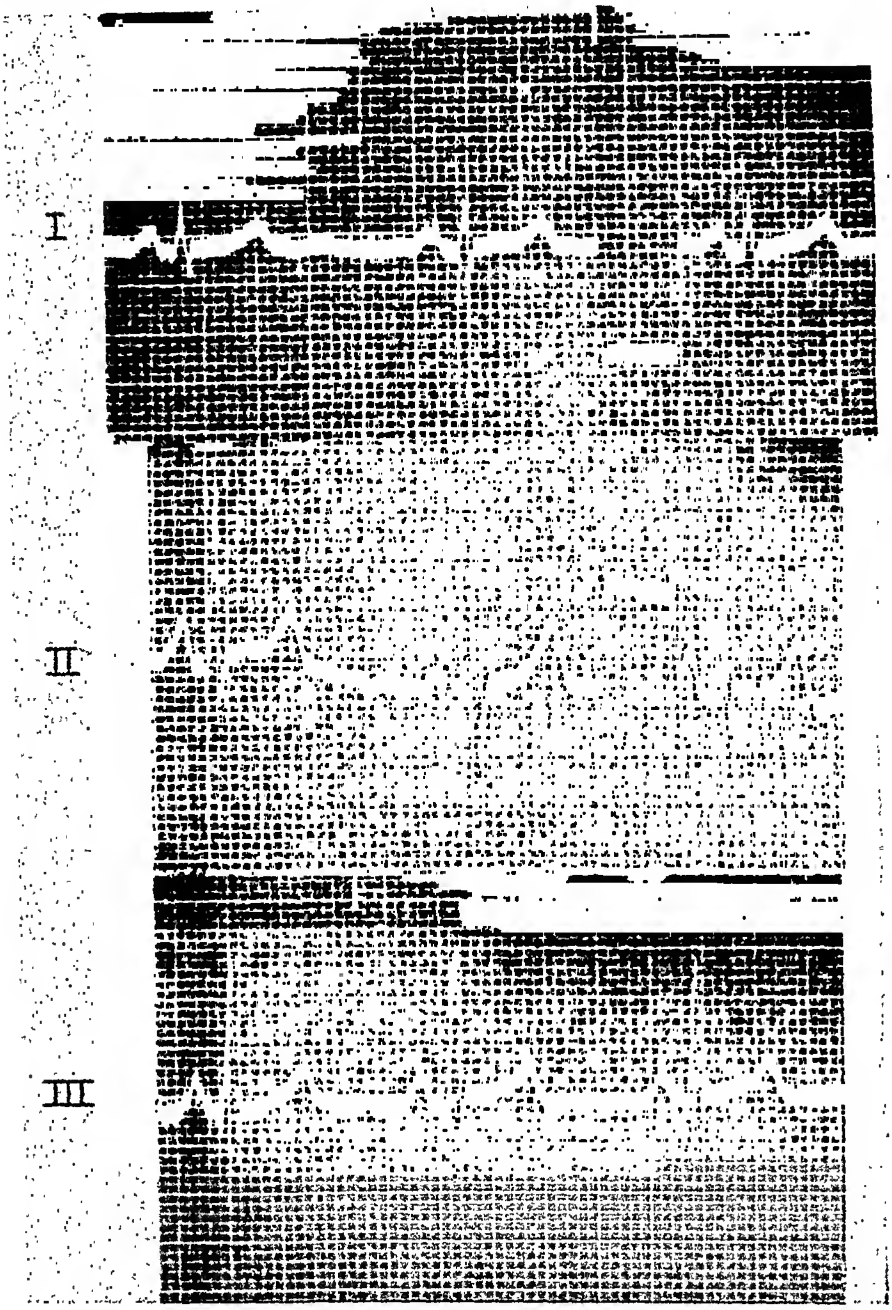

Fig. 6.—Electrocardiogram, three leads. The notched and high P waves, the elevation of the S-T_2 and S-T_3 segments, and the peaked T_2 and T_3 are found in rheumatic heart disease with mitral stenosis.

OBSERVATIONS FROM THE LITERATURE ON PULMONARY CHANGES IN MITRAL STENOSIS

Kerley[4] stated that in mitral stenosis the roentgenographic appearance of the lungs varies enormously. Occasionally, the combination of smaller end-on vessels and alveoli filled with "heart-failure cells" gives

the inhaled air, that most damage is probably produced by particles measuring between 1 and 3 μ, and that the development of silicosis depends on the amount of free silica in the air inhaled and the duration of exposure.

Pendergrass[2] and Twining[3] state that in making a differential diagnosis one must consider not only the miliary type of passive hyperemia and miliary tuberculosis, but also bronchiolitis, multiple pulmonary miliary abscesses, carcinomatosis, leucemic infiltration, disseminated actinomycosis, and Boeck's sarcoid.

The amount of silica excreted in the urine is no measure of the degree of pulmonary silicosis.[20] Except for examination of the lungs at necropsy, there are no further methods of establishing the diagnosis.[21]

PATHOLOGIC CHANGES IN MITRAL STENOSIS AND IN SILICOSIS

A comparison of the pathologic changes observed in the two diseases is of interest in that it suggests an explanation for the fact that the shadows cast by these fibrotic and proliferative lesions scattered throughout the lungs along the course of vessels and bronchioles are at times similar.

Gouley[22] studied the pathologic picture produced by parenchymal lung lesions in rheumatic fever and their relationship to mitral stenosis. He noted patchy interstitial fibrosis, and advanced lesions which were seen even without left auricular enlargement, particularly in mitral stenosis without mitral insufficiency. Moschcowitz[23] described the lung changes in arteriosclerosis affecting only the pulmonary circulation. This was associated with mitral stenosis in nine of his twelve cases. He stated that if the disease is of long standing, the increase in pericapillary connective tissue is so great that the alveolar wall becomes enormously thickened, and may thus give rise to a true interstitial infiltration. This thickening is due not only to the increase in connective tissue, but also to infiltration with fibroblasts. Parker and Weiss[24] described similar fibrotic changes in the lungs associated with long-standing mitral stenosis. Gloyne[25] described the nodular fibrotic changes in silicosis which are caused by minute aggregations of lymphoid tissue around the bronchioles, the branches of the pulmonary artery, the pulmonary veins, and the venous channels in the interlobar septa.

COMMENT

A case is presented in which the diagnosis of silicosis had previously been made because of abnormalities observed in repeated roentgenographic examinations.

Investigation showed that the patient had far less exposure than eight other persons who worked in the building nearer the presumed source of hazardous exposure, and that none of the others developed signs or symptoms of the disease. A search of the literature has shown that silicosis occurs only when persons are exposed to sufficiently high con-

in the dustiest part of the plant. Two of these men had very fine capillary fibrosis of the bronchial markings throughout both lungs, demonstrable roentgenologically; two others had extensive mottling throughout the lungs; the other two died from "myocarditis" (roentgenologic examination not made). Chapman[12] reported studies on three men exposed to a similar dust, who worked "in a very dusty atmosphere without protection." Symptoms appeared after eight, twenty-one, and twenty-nine months, respectively, of exposure. The first two men had roentgenologic evidence of silicosis, but the third, with similar symptoms, showed no evidence of silicosis on roentgenologic examination. Russell[13] noted the development of silicosis in a lens grinder who, in the course of his work, inhaled a fine quartz spray for eight months. Betts[14] noted the high mortality rate among a group of men employed in the dry grinding of quartzite. In portions of the mill the dust was so dense that it was impossible to recognize a person at a distance of a few feet, and an electric light looked like a spark. In a group of thirty men, with an average age of 30 years, the average survival period after starting work was twenty-nine months, and the average period of work was fourteen months. One man died within a year, after three months' exposure. Bloomfield and Dreessen[15] studied the incidence of silicosis in granite quarriers. The granite dust was 35 per cent quartz; 75 per cent of the particles were less than 2 μ in diameter, and 10 per cent were less than 1 micron. In a group with an average exposure to 112 to 144 million particles per cubic foot of air, no clinical or roentgenologic evidence of silicosis was found in any of thirteen men who worked less than five years, in eight of twelve who worked from five to nine years, in four of six who worked ten to nineteen years, or in one of five who worked more than twenty years. None of the men who were exposed to an average of less than 6 million particles per cubic foot had lesions, no matter how long they had worked. The Miners' Phthisis Medical Bureau Report[16] states that, in the gold mines of South Africa, where the dust is 80 per cent silica,[17] the average period of exposure before simple silicosis can be diagnosed is seven and one-half years, and the shortest period of exposure reported is two and one-half years.

Sayers, et al.,[18] reported on the incidence of anthracosilicosis among hard coal miners. Of the three hundred twenty-seven men who had worked less than fifteen years in the haulingways, where the dust contained 13 per cent silica and from 5 to 200 million particles per cubic foot of air, one developed silicosis. Rock workers worked in an atmosphere containing 35 per cent silica dust, with from 100 to 300+ million particles per cubic foot of air. None developed silicosis in less than two to three years; nine of seventy developed silicosis in less than fifteen years; twenty-five of thirty-nine in fifteen to twenty-four years, and thirty-two of thirty-five in twenty-five or more years. Sayers and Lanza[19] have concluded that the harmfulness of a given dust depends on the number of particles of free silica less than 10 μ in diameter in

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centrations of free silica for a sufficiently long period of time, and that no cases of acute silicosis have been reported in which symptoms appeared in as brief a period as that of the patient's exposure, that is, eighty-three days. Moreover, the miliary nodulation, which was simulated by the roentgenographic changes in this case, develops only after longer exposures than those needed for the development of acute symptoms of the disease.

A picture similar to that of silicosis is found not uncommonly in roentgenographic studies of miliary tuberculosis of the lungs, and in congestive heart failure, particularly that associated with mitral valve disease. There are also rarer diseases that simulate this picture, but there is no clinical evidence that this patient suffered from any of these rarer diseases or from miliary tuberculosis.

The pathologic changes in the lungs in silicosis and mitral stenosis were mentioned to suggest a reason for the fact that the roentgenographic picture in the two diseases may at times be similar.

The patient displayed physical, electrocardiographic, and roentgenologic evidence of mitral stenosis of a degree sufficient to cause the roentgenographic changes in the lungs.

The case study emphasizes that, although routine roentgenologic examinations may be of great value in detecting asymptomatic heart and lung disease, the definitive differential diagnosis of certain of these diseases can be made only on clinical grounds.

CONCLUSIONS

Repeated roentgenographic study of the lungs may not be sufficient to establish the diagnosis of silicosis.

On the one hand, the clinical diagnosis of pulmonary silicosis can be made despite the absence of roentgenographic evidence when there is a history of adequate exposure, when pulmonary symptoms and signs characteristic of the disease are present, and when other cause for the pulmonary symptoms and signs cannot be found. On the other hand, the roentgenographic evidence may be specific.

A case is presented in which hazardous exposure to silica dust did not occur, and roentgenologic changes suggestive of pulmonary silicosis proved to be due to pulmonary congestion resulting from mitral stenosis.

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800 feet. The towns of Aibonito and Orocovis are 2,000 feet above sea level; Barranquitas and Adjuntas are 1,700 feet, and Lares and Maricao, 1,400 feet, but San Juan, the capital, is only 100 feet above sea level.

The climate is tropical marine, slightly modified by insular influences. The effect of land and sea breezes causes land winds at night, and, consequently, somewhat lower night temperatures. This air drainage from the high altitudes in the interior of the island to the coast results in delightful night temperatures, especially during the winter months. The mean temperature for the entire island is 73° in winter and 79° in summer, with an average temperature of 76.6°.

The average annual rainfall is 72.62 inches. It is lowest in the south, with an average of 40 inches, and highest in the west, and around Luquillo, where it is more than 80 inches. The highest readings have been recorded at the Meteorological Station of Río Blanco, with 144.99 inches, and the lowest at Santa Rita, with only 29.62 inches. There is more rain during summer and autumn and less during winter and spring.

Notwithstanding the fact that San Juan has an average of 212 days a year with rain, there is an average of only five days a year entirely without sunshine. Except for the rains that occur in connection with infrequent tropical cyclones, rainfall comes in the form of brief showers which last a few minutes and are invariably followed by sunshine. At San Juan there is an annual average of 2,847 hours of sunshine, as contrasted with 300 to 500 hours in Paris and Berlin, and 800 hours in New York. There is also a high level of solar ultraviolet radiation.

The mean barometric pressure at San Juan from 1899 to 1930 was 29.90 inches; the lowest was 29.83, and the highest, 29.95 inches. The mean relative humidity for the same period was 78 per cent at 9:00 A.M., 76 per cent at noon, and 80 per cent at 9:00 P.M. We have, therefore, a stable barometric pressure and a rather high humidity.

In the year 1915 heart disease was the seventh most important cause of death in Puerto Rico, but since 1942 it has reached fourth place. Diarrhea and enteritis occupy first place, tuberculosis, second, and pneumonia, third. It is our impression, as suggested by Fernós,[4] in 1938, that in a not distant future, as a consequence of the improvement in the public health and sanitary conditions of the island—including better nutrition—the present three most important causes of death will become secondary health problems, and heart disease will be, as in most civilized countries, the chief cause of death.

Table I shows the mortality rates per 100,000 population for the seven most important causes in Puerto Rico during 1942 and 1943.

According to De la Pila Iglesias,[5] heart disease is the cause of 23.5 per cent of all deaths in Puerto Rico, and 38 per cent of all deaths in the United States. The same author states that, in the year 1938, there were 268.9 deaths from heart disease per 100,000 population in the

THE INCIDENCE OF HEART DISEASE IN PUERTO RICO

Statistical Analysis of 1,081 Cases

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We have already reported on the etiological types of heart disease in Puerto Rico. In 1939[1] we studied 155 cases at the Cardiac Clinic of Hospital Mimiya, 320 cases in 1941,[2] and, in 1942, while discussing a paper on "Syphilis in Puerto Rico," by Costa Mandry,[3] we gave our percentages in a series of 600 consecutive cardiovascular cases.

At present our series has reached 1,081 cases. All were native Puerto Ricans between 4 and 83 years of age; 90 per cent were white and 10 per cent were Negroes; 67 per cent were males, and 33 per cent, females. Private patients comprised 65.5 per cent of the series, and 34.5 per cent were ward patients, most of them agricultural laborers and veterans of the first World War. It was a heterogeneous group representing all economic and social strata, with a predominance of the upper, or intellectual and well-to-do, classes. Some of the patients came from distant parts of the island, but the majority were residents of San Juan or of neighboring towns.

The series included six cases of subacute bacterial endocarditis, which were classified as either rheumatic or congenital heart disease. Two cases of dextrocardia, three cases of acute bacterial endocarditis, and four cases of chronic cor pulmonale due to pulmonary schistosomiasis were not included.

All of the patients had electrocardiograms, and some had stethograms, phlebograms, and teleroentgenograms; cardiac measurements and cardiac function tests, such as the vital capacity, venous pressure, and circulation time, were also made. Either the Wassermann, Kline, or Kahn test was performed on most of the adult patients. When the diagnosis seemed evident, no laboratory data were obtained.

CLIMATOLOGY

Puerto Rico is a small, nearly rectangular island with an area of 3,400 square miles, situated between parallels of 18° and 19° north latitude. Its position with reference to the equator is approximately that of Hawaii, Jamaica, and St. Thomas. Mountain ranges, with a maximum elevation of 4,000 feet, extend obliquely across the island from the northeast to the southwest corners. They lie 25 miles to the south and 20 miles to the southeast of San Juan. Their average elevation is

Received for publication June 7, 1944.
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rheumatic fever (20 per cent), arteriosclerosis (17 per cent), and arteriolosclerosis or hypertension (9.3 per cent). These autopsies were made on people who belonged chiefly to the low social and economic groups of the island.

GENERAL CONSIDERATIONS

Table III gives the total number of deaths in Puerto Rico from diseases of the heart during the year 1942, as computed by the Bureau of Vital Statistics of the Insular Department of Health.

From the available mortality statistics, based on the *International List of Causes of Death,* it is impossible to distinguish the infectious from the degenerative varieties of cardiovascular disease. Cases of rheumatic carditis in people over 45 years of age have been included under list No. 92 as "Chronic Affections of the Valves of the Endocardium," and in list No. 95 with "Other Diseases of the Heart." Arteriosclerotic heart disease appears in list No. 93 with "Diseases of the Myocardium." Hypertensive cardiovascular disease does not appear in the List, and probably most of these cases were included under nephritis. The total number of deaths from all diseases of the heart in 1942 was 2,177, or 111.9 per 100,000. The death rate was lower in the rural (81 per 100,000), than in the urban, population (170.2 per 100,000) as is true in other places. At least, Table III points definitely to the fact that diseases of the myocardium, diseases of the coronary arteries, and angina pectoris—all of them of predominantly arteriosclerotic origin, degenerative types of cardiovascular disease—represent nearly 60 per cent of the total number of deaths from diseases of the heart.

According to Cossio,[7] Argentina, with a population of 13,000,000, has 260,000 cases of diseases of the heart, an average of 2 per cent. Diseases of the heart were found in 1.4 per cent of 6,806 soldiers 20 years of age, in 2.4 per cent of 10,000 school children, and in 3 per cent of railway employees whose average age was 35 years. A similar average of 2 per cent for the general population is given by Chavez[8] for Mexico, and

TABLE III

TOTAL DEATHS IN PUERTO RICO FROM DISEASES OF THE HEART
1942

INTER. LIST NO.	CAUSES OF DEATH	URBAN		RURAL		TOTAL	
		DEATHS	RATE	DEATHS	RATE	DEATHS	RATE
90	Pericarditis	4	0.6	---	---	4	0.2
91	Acute endocarditis	16	2.4	9	0.7	25	1.3
92	Chronic affection of the valves and endocardium	176	26.1	154	12.1	330	17.0
93	Diseases of the myocardium	475	70.4	498	39.2	973	50.0
94A	Diseases of the coronary arteries	159	23.6	84	6.6	243	12.5
94B	Angina pectoris	34	5.0	44	3.5	78	4.0
95	Other diseases of the heart	284	42.1	240	18.9	524	26.9
90 to 95	All diseases of the heart	1,148	170.2	1,029	81.0	2,177	111.9

TABLE I

PUERTO RICO MORTALITY STATISTICS
DEATHS PER 100,000 POPULATION

CAUSE	1942	1943
Diarrhea and enteritis	331.4	286.6
Tuberculosis	244.5	230.1
Pneumonia	141.5	121.2
Heart disease	111.9	102.4
Malaria	99.4	59.0
Nephritis	98.7	80.7
Cancer	54.8	50.1

United States, 119.8 in Puerto Rico, 113.3 in Hawaii, and 128.1 in the state of Oklahoma; the latter was the lowest figure for all the states in the Union.

In a series of 1,259 complete autopsies on native Puerto Ricans, 128 persons (10 per cent) were found to have died from cardiovascular disease, whereas large series of autopsies in the United States give a percentage average of 38 for diseases of the heart. The incidence of the various kinds of cardiovascular disease encountered in the group of 128 persons was given by Koppisch[6] as follows: syphilitic heart disease, 38 cases (30 per cent); rheumatic heart disease, 26 cases (20 per cent); arteriolosclerosis, 12 cases (9.3 per cent); arteriosclerosis, 22 cases (17 per cent); congenital lesions, 10 cases (7.8 per cent); acute bacterial endocarditis, 7 cases (5.5 per cent); subacute bacterial endocarditis, 10 cases (7.8 per cent); one case (0.7 per cent) of diphtheritic myocarditis; and one case (0.7 per cent) of hyperthyroidism. There was also one case (0.7 per cent) of chronic endocarditis of unknown cause.

Twenty (over 50 per cent) of the 38 patients with syphilitic heart disease had a complicating aortic aneurysm, and 13 (over 50 per cent) of the 22 patients with arteriosclerosis were found to have coronary occlusion or myocardial infarcts.

According to Koppisch's[6] post-mortem studies of 128 cases (Table II), syphilis is the most important cause of death (30 per cent), followed by

TABLE II

CARDIOVASCULAR DISEASE IN PUERTO RICO
ANALYSIS OF 1,259 AUTOPSIES
(Koppisch, 1944)

CAUSE	NUMBER OF CASES	%
Syphilitic heart disease	38	30.0
Rheumatic heart disease	26	20.0
Arteriolosclerosis	12	9.3
Arteriosclerosis	22	17.0
Congenital heart disease	10	7.8
Endocarditis, bacterial, acute	7	5.5
Endocarditis, bacterial, subacute	10	7.8
Myocarditis, diphtherial	1	0.7
Hyperthyroidism	1	0.7
Endocarditis, chronic, cause unknown	1	0.7
	128	

TABLE IV

	ARGENTINE 10,000 CASES COSSIO[7] 1943 (%)	MEXICO 2,400 CASES CHAVEZ[8] 1942 (%)	NEW ENGLAND WHITE[15] 1944 (%)	NEW YORK PARDEE[16] 1941 (%)	VIRGINIA 2,607 CASES PORTER 1939-1942 (%)	LOUISIANA 2,096 CASES MUSSER[17] 1942 (%)	PUERTO RICO 1,081 CASES SUÁREZ 1937-1944 (%)
Syphilis	7.7	11.2	2.0	3.0	9.0	8.3	6.1
Rheumatic	18.2	41.0	38.0	32.0	13.0	8.2	17.4
Hypertension	23.7	13.6	28.0	36.0	36.0	57.6	22.8
Arteriosclerosis	--	28.3	--		39.0	24.1	39.9
Hypothyroid	5.8	--	--	--	--	.04	2.8
Hyperthyroid		1.4	0.2	--	--	.2	2.6
Congenital	2.4	1.8	2.0	--	2.0	.7	1.0
Avitaminosis	--	--	--	--	--	.2	.9
Functional	--	--	--	--	--	--	5.8
Miscellaneous	3.7	2.0	--	--	--	--	.7

where he found a percentage of 41, by White[15] in New England (38 per cent), and by Pardee[16] in the New York Heart Clinics (32 per cent). It is higher than that given by Musser[17] for the Louisiana Charity Hospital in New Orleans (8.2 per cent).

In evaluating our figures, we should bear in mind the fact that only 64 patients (5 per cent) in our series of 1,081 cases were between 4 and 20 years of age. A larger number of children would undoubtedly have given a higher rate of rheumatic disease (Table V).

TABLE V

AGES (YR.)	NUMBER OF CASES	PER CENT
4 to 20	64	5
21 to 50	505	47
51 to 83	512	48

Syphilis.—Table IV shows that cardio-aortic syphilis is not as frequent in Puerto Rico as we have been led to believe. In the series studied for a number of years, the incidence has varied between 10 and 5.9 per cent, and the average for the total number of cases studied is 6.1 per cent. This figure is higher than that reported for the New England States (2 per cent) and for New York (3 per cent), but it is lower than that of Argentina (7.7 per cent), Mexico (11.2 per cent), Virginia (9.0 per cent), and Louisiana (8.3 per cent). Both Francisco and Koppisch give a higher incidence for syphilitic heart disease in Puerto Rico, 12.8 per cent and 30 per cent, respectively. We should recall again that their material was obtained principally from the lowest social and economic groups of our population.

Hypertension.—The incidence of hypertension, unaccompanied by apparent arteriosclerosis or angina pectoris, is 22.8 per cent (Table IV), as compared with 23.7 per cent in Argentina, 13.6 per cent in Mexico, 28 per cent in the New England States, 32 per cent in New York, and 36 per cent in Virginia. The highest incidence of hypertension is that reported in Louisiana, 57.6 per cent.

by Parran[9] for the United States. In Puerto Rico we do not have similar data for comparison, except that, of 31,600 men between 18 and 38 years of age who had been carefully examined, 1.5 per cent were found to be suffering from diseases of the heart.

Rheumatism.—The prevalence of rheumatic heart disease is dependent upon many factors, among which are climate, geographical location, racial or hereditary predisposition, and living conditions.

The five most important theories are that it is caused by: (1) a specific, nonhemolytic streptococcus; (2) tissue hypersensitiveness to the streptococcus; (3) infection superimposed on vitamin "C" deficiency (Rinehart); (4) a hemolytic streptococcus (Coburn), and (5) a filtrable virus (Schlesinger, Signy, Ames, and Barnard). At present the evidence in favor of the beta-hemolytic streptococcus group "A" predominates.

In connection with this theory, it is interesting that Morales-Otero, Damin, and Pomales[10] found a smaller number (only 4 per cent) of positive throat cultures for group "A" beta-hemolytic streptococci in Puerto Rican troops than in an approximately equal number of Continental troops stationed on the island for over one year. In 28.8 per cent of the latter there were positive throat cultures. This work, and that of Pomales-Lebron and Morales-Otero[11] on rhesus monkeys, furnishes additional evidence "to support the statement that the proportion of group "A" hemolytic streptococci found in the normal throat in the tropics is lower than that obtained from a similar source in temperate regions."

It has been stated that rheumatic fever does not exist, or is rare, in the tropics. So it was thought in Puerto Rico, until Dr. Hans Smetana, formerly pathologist of the School of Tropical Medicine, found, on June 28, 1930, the first case of rheumatic fever, with Aschoff's bodies, in a 15-year-old Puerto Rican boy. It may be that the clinical manifestations of rheumatic fever are mild and indefinite in the tropics, and that the joint symptoms are either mild or absent altogether, but rheumatic heart disease is far from being rare. The work of Chavez in Mexico, of García Carrillo[12, 13] in Costa Rica, of Francisco[14] and Koppisch, and our own observations in Puerto Rico prove conclusively that the incidence of rheumatic carditis in tropical and subtropical regions is equal to, or higher than, the incidence in colder climates.

The incidence of rheumatic heart disease in our own series was 24.7 per cent in 1941, when only 320 cases had been studied, and 17.4 per cent at present, in a series of 1,081 cases (Table IV). Francisco reports 32 per cent in a group of 125 cases at the Arecibo District Charity Hospital, and Koppisch's anatomicopathologic data reveal an incidence of 20 per cent in 128 deaths from diseases of the heart. Our incidence is, therefore, about the same as that reported by Cossia in Argentina (18.2 per cent) and by Porter (13.0 per cent) in Virginia. It is lower than that reported by Chavez in Mexico City (7,000 feet above sea level)

of meat is so very low (33.4 pounds, or 15 kg., per capita), coronary disease, including angina pectoris, is not at all infrequent (15 per cent), with a death rate of 16.5 per 100,000 population. Chavez seems to favor a racial factor, which operates through a nervous mechanism, in the production of hypertension, angina pectoris, and coronary occlusion, and he bases his assertion on the low incidence of the senile degenerative changes among the Indians of Mexico. Quoting from him: "For centuries the Mexican Indian has lived a slow and unharrassed life. His manual labor may sometimes be strenuous, but he knows nothing of uneasiness and anxiety. His philosophy of life is conformist, if not fatalistic. He has a well-balanced nervous system, which protects him

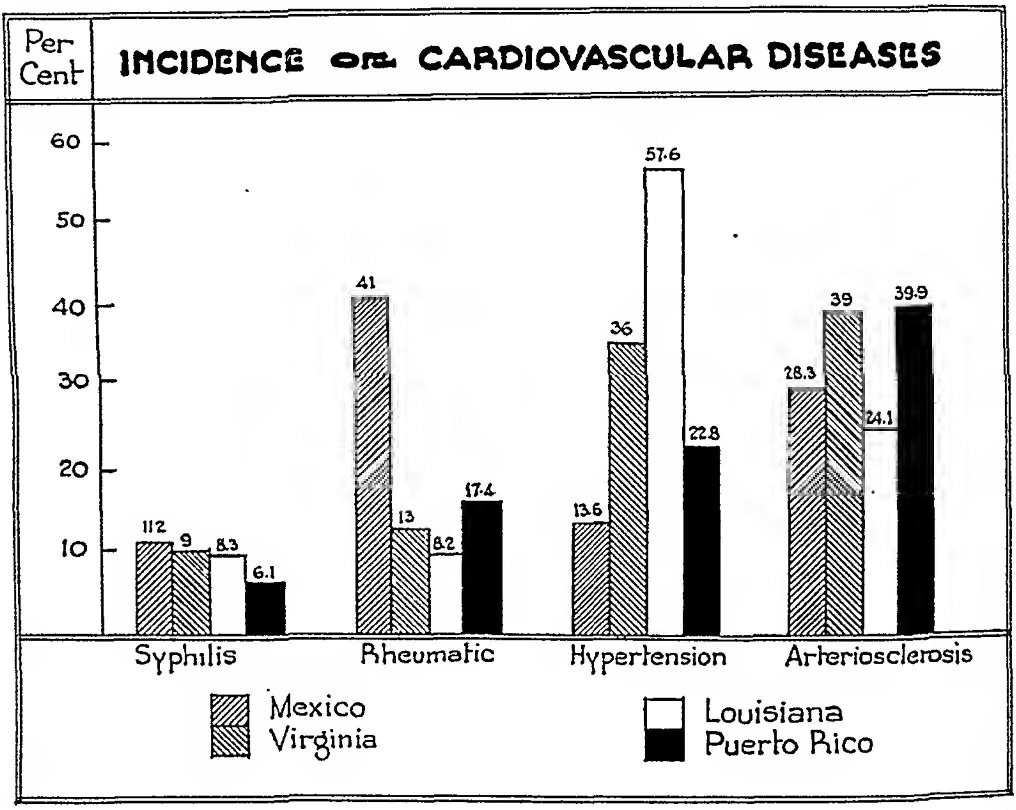

Fig. 1.

from the ordinary impacts of life, and he knows nothing of psychasthenia. What we call civilized living either does not reach him, or if it does, fails to traumatize his mind." We are inclined to believe that a similar nervous stability and a similar fatalistic philosophy of life might explain, in part, at least, the lower incidence of angina pectoris and coronary disease in our "jibaro" population (Fig. 1).

SUMMARY AND CONCLUSIONS

1. We have described the geographical position, topography, and climatology of Puerto Rico as a factor to be considered in the incidence of rheumatic fever and other diseases of the heart.

If we add the cases of hypertension to those of arteriosclerosis, we would have an incidence of heart disease due to senile degenerative changes of about 62 per cent.

Arteriosclerosis.—The expectancy of life in Puerto Rico, as computed from abridged life tables by J. L. Janer, Statistician of the Insular Department of Health for the years 1939, 1940, and 1941, and in accordance with the Reed-Merrell method, is only 46 years from birth (45.10 for the male population and 47.29 for the female population). When the age of 5 years is reached, life expectancy rises to 52.85 years (52.1 for males and 53.8 for females). The life expectancy in the United States, in 1937, was 62.25 years, 16 years more than in Puerto Rico.

According to Morales-Otero,[18] the official census of 1940 shows that 40.6 per cent of our population is made up of children below the age of 15 years, and that people over 65 years of age make up only 3.4 per cent of the total population. The group of adults over 65 years of age is twice as high in the United States, where it reaches an average of only 6.8 per cent.

Arteriosclerosis is primarily a disease of old age, and the population of Puerto Rico is pre-eminently young. Notwithstanding this fact, the incidence of arteriosclerosis in our series was 39.9 per cent (Table IV), which is equal to that of Virginia (39 per cent) and higher than that of Mexico (28.3) and Louisiana (24.1 per cent).

The incidence of arteriosclerosis and hypertensive heart disease, as given by Francisco and Koppisch, is lower than ours. The former gives figures of 20 and 25.6 per cent, respectively; the latter's figures are 17 per cent for arteriosclerotic heart disease and 9.3 per cent for arteriolosclerosis.

There were 163 cases of coronary insufficiency (15.0 per cent) in our series of 1,081 cases. Roughly, 40 per cent of the patients with arteriosclerotic heart disease showed clinical and electrocardiographic evidence of myocardial infarction.

It is a well-known fact that, in private practice, rheumatism and syphilis are less frequent than among ward patients; on the other hand, coronary disease, including angina pectoris, is much more common among private than among hospital patients.

The cause of atherosclerosis remains unsettled. The theory of altered lipid metabolism has many advocates. Some attribute the low incidence of arteriosclerosis, angina pectoris, and coronary sclerosis among the Chinese[19] to the low intake and quality of the fat in their diet. Others have suggested that a diet in which meat predominates is an important factor in atherosclerosis. However, nutritional surveys in Argentina, the United States, and Puerto Rico do not substantiate this hypothesis. The consumption of meat is 107 kg. per capita in Argentina, where the incidence of coronary disease is only 29.6, whereas, in the United States, with a lower meat consumption (66 kg. per capita) the incidence of coronary disease is 37.7 per cent, and in Puerto Rico, where the consumption

THE EFFECT OF LANATOSIDE C UPON THE PHYSIOLOGIC STATE OF ORGANICALLY DISEASED HEARTS BEFORE SYMPTOMS AND SIGNS OF HEART FAILURE APPEAR

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IT WOULD be difficult to conceive that anyone who has read a recent paper which is available to all cardiologists[1] would doubt the efficacy of the glycosides of digitalis in helping to relieve the symptoms and signs of heart failure in the presence of normal sinus rhythm. On the other hand, there is still doubt as to the value of digitalis in cases of organic heart disease in which the usual symptoms and signs of heart failure have not developed. Christian[2] felt that cardiac enlargement was retarded, and that patients with evidence of cardiac disease, but without symptoms or signs of cardiac insufficiency, were capable of greater activity without the development of symptoms of cardiac insufficiency when approximately 0.2 to 0.3 Gm. of digitalis leaves per day was administered prior to the development of symptoms and signs of heart failure. Christian's conclusions were drawn purely from his clinical observations.

Cloetta,[3] who studied the effect of digitalis on the heart of the rabbit, came to the conclusion that the dilatation and hypertrophy of rabbits' hearts with experimental aortic insufficiency never reached the same degree that occurred in the hearts of rabbits with experimental aortic insufficiency without digitalis treatment. Cloetta also was convinced from his experiments on rabbits that the absolute energy reserve of hearts with aortic insufficiency was nearly normal if digitalis was administered, whereas, if digitalis was not administered, the hearts were much more rapidly exhausted. He felt that he had proved that the capacity for work of hearts that were treated with digitalis was nearly double that of untreated hearts.

Cohn and Stewart,[4] by means of experiments on dogs in which defects in the mitral valve had been produced by operation from two to six years before the experiments were performed, found that the cardiac area, as measured roentgenologically, had increased from 5 to 94 per cent. From 25 to 30 per cent of the calculated oral lethal dose of digitalis was injected intravenously into these animals. There were a decrease in the size of the heart and a decrease in the cardiac output for the first twenty-

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Partial abridgement of thesis submitted by Dr. Erickson to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Medicine. This study was aided by grants from the American Medical Association and the Sandoz Chemical Company.

Received for publication June 19, 1944.

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2. We have made ample use, not only of the vital statistics of the Department of Health, but also of the figures obtained and studies made by other observers in the island.

3. We have presented statistical studies based on 1,081 cardiovascular cases.

4. We have compared our own figures with those of Argentina, Mexico, the New England States, and the states of New York, Virginia, and Louisiana.

5. The incidence of the four most important etiological types of heart disease in Puerto Rico is as follows: syphilis, 6.1 per cent, rheumatic fever, 17.4 per cent, hypertension, 22.8 per cent, and arteriosclerosis, 39.9 per cent.

6. It appears from this study that climate, per se, is not a deciding factor in the prevalence of either syphilitic or rheumatic heart disease, or of heart disease due to senile degenerative changes.

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In this paper we shall attempt to show that a glycoside of digitalis will improve the function of the heart in cases of organic heart disease in which, as yet, symptoms and signs of heart failure have not been present. We also shall compare the response of the normal heart to the same glycoside of digitalis, in an attempt to show that the function of the heart of a normal person is impaired by digitalization.

The glycoside of digitalis employed in this study was lanatoside C. We made use of this glycoside because we had used it in previous studies on cases of organic heart disease in which there were both the symptoms and signs of severe heart failure, and it had proved efficient in relieving the symptoms of heart failure in cases in which normal sinus rhythm was present. Lanatoside C is a crystalline glycoside, and its potency will always remain the same because the enzymes that destroy digitalis have been removed. There is no reason to believe that the same results would not have been obtained with other glycosides of digitalis, although there might, of course, be marked quantitative differences.

In order to obtain a clear conception of heart function and the indications for cardiac therapy, it seems essential to consider the heart as a working machine with a variable mechanical efficiency which should be maintained at the highest practicable level. The heart is a mechanical pump which converts the energy liberated by oxidation within the muscle cell into mechanical work. When the heart fails, one of two things must happen if the heart is confined in a rigid chamber which will prevent dilatation. Either the mechanical work done must decrease, and the total energy liberated by oxidation during contraction (oxygen consumption) remain the same, or the total energy liberated during contraction (oxygen consumption) must decrease, and the mechanical work decrease proportionately. The ratio of mechanical work done by a machine to the total energy liberated in the process is the mechanical efficiency, or, applied to the heart, the work of the heart divided by the oxygen consumption. Therefore, one can say that in heart failure either the mechanical efficiency decreases, in which case the work of the heart is carried out at the expense of greater oxygen consumption, or the work of the heart decreases at the same, or a greater, rate, than the oxygen consumption, in which case the mechanical efficiency remains the same or decreases. Decherd and Visscher[8] and Moe and Visscher[9] have shown that the mechanical efficiency of the heart of the experimental animal decreases in spontaneous heart failure.* Fahr and Buehler[10] have shown the same thing for the heart poisoned by cardiac poisons. Katz and Mendlowitz[11] disagreed with this conception, but the work of Moe and Visscher[9] discounted their conclusions.

Studies on the heart-lung preparation therefore indicate that myocardial failure consists, in essence, of an alteration in the energy-

*As a matter of fact, Starling and Visscher[7] showed this in their paper, but did not emphasize the fact that the decrease in mechanical efficiency was the cause of heart failure.

four hours after the intravenous injection. As the action of the digitalis began to decrease, the cardiac output returned to normal or even increased, although the heart sometimes continued to be smaller than it had been in the beginning. In our opinion, 25 to 30 per cent of the calculated oral lethal dose of digitalis, given intravenously, is a number of times the optimal digitalizing dose, and is close to a toxic dose. Kabat and Visscher[5] have shown that, when optimal doses of digitalis are applied to the tortoise heart by perfusion, there is an increase in the mechanical efficiency of the heart muscle without a change in elasticity, but when larger doses are given there is an increase in elasticity with a decrease in the work of the heart. We believe that, in the dogs' hearts studied by Cohn and Stewart, the proper therapeutic concentration of digitalis was in all probability not obtained until several days after the administration of the drug, and at this time it was noted in their experiments that, although the cardiac size was still reduced, the cardiac output was increased to the original, or greater than original, values, which indicated a favorable therapeutic response.

Stewart, Crane, Deitrick, and Thompson[6] studied the effect of giving digitalis in therapeutic doses to seventeen patients suffering from organic heart disease who had not had congestive failure. These patients had heart disease of either Type I or Type IIA, as defined in the publication entitled *Criteria for the Classification and Diagnosis of Heart Disease,* issued by the Heart Committee of the New York Tuberculosis and Health Association. These authors measured the cardiac output by the Grollman acetylene method. Roentgenograms of the cardiac silhouette were made, the cardiac area was measured, and the volume of the heart was estimated by the Bardeen formula. In their experiments, the work of the left ventricle per beat was calculated from the stroke output times the mean arterial blood pressure. These measurements were first made before digitalis was given. Then from 1.6 to 1.8 Gm. of digitalis leaves were given in twelve hours. Twenty-four to forty-eight hours after the digitalis was given, the measurements were repeated. Four of the patients showed an increase in cardiac output and a decrease in cardiac size. Seven patients showed a decrease in cardiac output as well as a decrease in cardiac size, and six patients showed no change in cardiac output or in cardiac size. The work of the left ventricle per beat was increased in every case, no matter whether the output was increased, decreased, or unaltered. If this work is interpreted in the light of Starling and Visscher's work,[7] namely, that the oxygen consumption of the heart is a function of its diastolic volume, one can state that these investigators showed that the mechanical efficiency of these compensated hearts was increased in every instance after digitalis was administered. As a result of these investigations, it would seem probable that the clinical impression of Christian, namely, that digitalis actually is of benefit when the heart is enlarged and compensated, is true.

ventricle if the circulation is to be maintained. In the heart of a normal dog, the mean pressure in the pulmonary artery is about a fourth of that in the aorta. Therefore the physiologist, in calculating the total work of the heart, usually multiplies the output of the left ventricle by the mean blood pressure in the aorta, and adds 25 per cent to this figure as a measure of the total work of the heart. The work of the human heart-beat, therefore, can be set down as $W = k_2SP$, where k_2 is a constant, S is the stroke output of the left ventricle, P is the mean blood pressure in the aorta, and W is the work of the heart per beat.

From the formula for total energy liberation and work of the heart, the mechanical efficiency with which the heart functions can be ascertained by the equation $\frac{k_2SP}{k_1(V_d - B)} = E_m$, where E_m is the mechanical efficiency. The quotient of $\frac{k_2SP}{k_1(V_d - B)}$ can be changed to $K\frac{SP}{V_d - B}$, so that the final formula for the mechanical efficiency is $E_m = K\frac{SP}{V_d - B}$, where K is a constant, S the stroke output of the left ventricle, P the mean blood pressure in the aorta, and V_d the diastolic volume. The constants K and B cannot be measured on human patients, but S, P, and V_d can. Percentage changes in the quotient $\frac{SP}{V_d}$ will always be less than percentage changes in $\frac{SP}{V_d - B}$, or the mechanical efficiency. We have called the quotient $\frac{SP}{V_d}$ the efficiency index, or E_i. It is to be emphasized that the efficiency index of a human heart is a relative, and not an absolute, expression of true mechanical efficiency. Consequently, the efficiency index cannot be used to compare the state of heart function among any group of persons; however, it will reflect accurately changes in the efficiency of the heart of a given person, and this is of primary importance in our study. We also know that the percentage changes in this efficiency index, as measured by us, are always less than the actual percentage changes in mechanical efficiency.

We measured the stroke output, S, by means of the Keys and Friedell[14, 15] method. This method is based upon changes in the frontal silhouette area of the heart, as ascertained roentgenkymographically. By this technique, the diastolic volume of the heart is ascertained very accurately through the use of a formula which relates the frontal silhouette area of the heart to the cardiac volume. Roentgenkymograms record only the changes in the frontal area of the heart that take place in the transverse diameter during systole. This systolic frontal area is then converted into the so-called systolic volume of the heart. The difference between these two volumes is a function of the true systolic output of the ventricles, and, when multiplied by a constant, gives the stroke output of the left ventricle. The stroke output of the left ventricle of fifty-four normal persons was ascertained by Keys and Friedell by the Groll-

utilizing, and not the energy-liberating, mechanism of the heart, and that the correction of this defect should be the objective in the treatment of myocardial disease. Peters and Visscher[12] and Moe and Visscher[13] have shown that the glycosides of digitalis correct this defect by increasing the mechanical efficiency of the spontaneously failing heart, and Fahr and Buehler[10] have shown that lanatoside C does the same for hearts poisoned with cardiac toxins. Fahr and Buehler have demonstrated that, when a glycoside of digitalis (lanatoside C) improves the mechanical efficiency of a failing heart, the venous pressure on both the left and right side of the heart, which was elevated during heart failure, decreased toward the normal.

Quantitative studies of the changes in heart function and their response to digitalis can now be carried out on human hearts by the use of roentgenkymography. This actually serves as a cardiometer for the human heart, in that the systolic and diastolic volume can be measured and the stroke output can be calculated from the change in volume. In order to understand the results obtained by this technique it is necessary to elaborate a little on the experimental methods and their physiologic significance.

Starling and Visscher[7] showed that the oxygen consumption, or total energy liberation of the heart, was a function of the diastolic length of the fibers of the heart muscle. They showed that the ratio of a given change in oxygen consumption (ΔO_2) to the corresponding change in diastolic volume (ΔV_d) was a constant (throughout a very large range of change in diastolic volume), or, expressed in the form of an equation, $\frac{\Delta O_2}{\Delta V_d} = k_1$. Therefore, we can set up the equation, $O_2 = k_1 \left(V_d - \frac{b}{k_1}\right)$, where O_2 is the oxygen consumption per beat, V_d is the diastolic volume of the heart at the time of the cardiac contraction which can be measured accurately in man by means of the roentgenkymograph, and b is a constant. k_1 is a constant which will differ for each heart, but has a constant value for any given heart. We can replace $\frac{b}{k_1}$ by B, and the formula for oxygen consumption becomes $O_2 = k_1 (V_d - B)$, where B is a constant which equals the volume of the undistended heart in diastole, or, in other words, when no intraventricular pressure is present during diastole. Starling and Visscher[7] proved this fundamental law of the heart on hearts which were only mildly failing spontaneously, but Fahr and Buehler[10] proved that the same holds true for hearts severely injured by cardiac poisons. We believe that this is a fundamental law of the heart; in fact, it is the real "law of the heart."

The work of any chamber of the heart per beat is the output of blood per beat times the mean blood pressure against which the blood is ejected. For this type of study, that part of the work of the heart which is represented by the kinetic energy of the blood thrown out of the heart can be neglected because it is of the order of magnitude of 3 per cent of the total. The output of the right ventricle must equal that of the left

TABLE I

HEART FUNCTION IN SEVERE HEART FAILURE BEFORE AND AFTER TREATMENT

TIME OF OBSERVATION	VENOUS PRESSURE	DIASTOLIC VOLUME (V_d)	STROKE OUTPUT (S)	WORK IN KG. METER PER BEAT (SP)	EFFICIENCY INDEX (E_i)	CHANGE (%)	CASES
Effect of lanatoside C on heart failure							
Before lanatoside C	20.3	1.021	44.4	67.6	66.2	+46	10
½ to 2 hours after lanatoside C	15.0	0.980	54.0	94.7	96.6		10
Effect of lanatoside C plus rest in bed							
Before lanatoside C	19.0	0.990	42.3	72.4	73.0	+70	7
After lanatoside C and 3 to 6 weeks rest in bed	6.2	0.756	55.8	94.0	124.0		7

described, the fifth, the average work of the left ventricles, and the sixth, the average efficiency index as calculated from these data. In the seventh column we have tabulated the percentage change in the efficiency index. The number of cases studied is given in the eighth column. The percentage change in efficiency index for this part of the experiment indicates the effectiveness of lanatoside C alone. Average values are shown for seven of the cases in which investigation was carried out just before the patients were dismissed from the hospital, that is, after lanatoside C had been given and the patients had been kept on an approximate maintenance dose of lanatoside C, in addition to rest in bed and other measures used in treating heart failure, for three to six weeks. The percentage change in the efficiency index for this part of the experiment represents the results of combined treatment with lanatoside C and rest in bed. This table demonstrates that the intravenous administration of lanatoside C alone increases the efficiency index about 45 per cent within a half to two hours after administration. It also demonstrates that three to six weeks of rest in bed, in addition to the intravenous administration of lanatoside C and daily oral doses of 0.75 mg. of lanatoside C, increases the mechanical efficiency another 24 per cent. The data contained in this table show indirectly that, during the development of heart failure in these severe cases, the mechanical efficiency had decreased an average of 70 per cent. Correlated with this fall in mechanical efficiency, there was an average increase in the venous pressure of 13 cm. of water. The venous pressure decreases with treatment and the concomitant rise in mechanical efficiency.

These data prove that, in the human being, as well as in the animal, the fundamental factor in heart failure is a decrease in the percentage of the total energy liberated which is available for mechanical work during contraction, and that digitalis acts by allowing the heart to convert more of its available energy into useful work. Starr and his co-workers,[17] who studied the action of digitalis in cardiac decompensation,

man acetylene technique and by their roentgenkymographic method, and a very close correlation was found.

This is not the place to go into a long discussion of the relative merits of the various methods of measuring the stroke output of human hearts. One advantage of the method of Keys and Friedell over all the other methods, with perhaps the exception of the ballistocardiograph, is that it measures the regurgitant, as well as the forward flowing, components of the stroke output of the left ventricle when aortic insufficiency or mitral insufficiency is present. All of the foreign gas methods, and even the celebrated Fick method, which is usually used as a measure of the accuracy of any stroke output method, fail to measure the amount of blood that shuttles back and forth between the aorta and left ventricle in aortic insufficiency and between the left ventricle and the left auricle in mitral insufficiency. Inasmuch as many patients with heart disease will have relative or organic mitral insufficiency, and some of them will have aortic insufficiency, we believe that the method of Keys and Friedell gives a better measure of relative changes in the stroke output of the left ventricle than any foreign gas method or the Fick method. Therefore, for our purpose, which is to measure percentage changes in the efficiency of the heart, it is of no consequence whether the Keys and Friedell constants, or other constants, should be used in any given case. As long as the same technique in recording tracings and computing the silhouette area is used, the results obtained by the method of Keys and Friedell for measuring the output and volume of the heart accurately reflect changes in these functions in the same case, and reflect relative differences in these functions in a series of cases.

We measured the systolic and diastolic blood pressure by the Korotkow auscultatory method. The diastolic volume, V_d, was measured by applying the Keys and Friedell formula to the diastolic silhouette area of the heart as obtained roentgenkymographically. In any series of roentgenkymograms on the same patient, the vertical heights of the tracings were kept constant, for it is impossible to ascertain changes in this direction on the horizontal slit film with any degree of accuracy. We believe that the diastolic volume, as ascertained by this method, is very close to the actual volume of the heart, and there can be little doubt that percentage changes in diastolic volume, as obtained by this method, are accurate.

When facilities for measuring the diastolic volume and stroke output of the human heart are available, it can be shown that the mechanism of heart failure and the response to digitalis are the same as in animal experiments. Table I summarizes the data from the paper of LaDue and Fahr,[16] in which quantitative changes in the function of the heart were measured by the roentgenkymogram to ascertain the effects of lanatoside C on heart failure. The first column shows the time of observation, the second, the average venous pressure, the third, the average diastolic volume, the fourth, the average stroke output as obtained by the method

level of the right auricle with the patient in a reclining position. The test was repeated, and the average of the two readings was taken as the circulation time. As the arm-to-tongue circulation time, we used the time from the start of the injection to the time the patient announced the onset of a hot sensation in his throat.

According to Goldberg's[21] study of 156 patients, the upper limit of normal for this method is sixteen seconds. However, none of the patients with clinical evidence of heart failure had a circulation time of less than twenty seconds. Spier, Wright, and Saylor[22] said that the normal circulation time with calcium gluconate varies between seven and twenty-two seconds. Patients with circulation times up to twenty seconds were selected, provided their venous pressure was normal and no congestive râles could be heard. Seventy-five per cent of the patients had a circulation time of less than sixteen seconds; the remainder had a circulation time in the transition zone (sixteen to twenty seconds).

All observations were made between 5 and 7 P.M. The patients were instructed to eat a light lunch and to take nothing but water by mouth until they reported for the roentgenkymographic studies. The patient was placed in front of the roentgenkymograph in a standing position, and was allowed to rest in this position until the pulse rate became stabilized for five minutes. During this time the patient's blood pressure was recorded. The patient was then instructed to breathe moderately deeply and was ordered to stop breathing during the phase of mid-inspiration. While the patient held his breath, a roentgenographic exposure of two and one-fourth seconds was made with the tube target at a distance of 36 inches (91.4 cm.) from the film. The blood pressure was again measured, and, with the patient in the same position, a duplicate roentgenkymogram was made within five minutes of the original one. The roentgenkymograph was fitted with an electric timer, and the pulse rates were calculated directly from the roentgenkymogram.

Moderate inspiration was selected as the standard condition for kymographic estimation of cardiac function because the best visualization without alteration of the stroke output was attained. Keys and Friedell[14, 15] found that it is unnecessary to maintain extreme constancy in respiratory conditions, for a considerable latitude in the respiratory phase has relatively little effect on the heart volume and the stroke output as calculated by their method. It is essential to guard only against abnormally high or low intrathoracic pressures, such as occur with forced inspiration or expiration.

The response to exercise of the patients whose ability to exercise was not limited by anginal distress was then measured. The exercise consisted of ascending and descending a three-step platform with a total rise from the ground of 2½ feet (76.2 cm.) a calculated number of times in a given period of time. The amount of work to be performed was determined from tables constructed by Master and Oppenheimer,[23] which give the foot-pounds of work per minute that a normal person of stated weight, age, and sex can perform with a return of pulse rate

also showed that when the diastolic volume was plotted against the work of the heart there was a tendency for the resultant value to move closer to the normal circulatory zone, as defined by Starr, in every instance, whether the stroke output was increased, decreased, or remained the same. Starr's method of plotting actually gives an expression which is related to changes in the mechanical efficiency of the heart under treatment, although this was not mentioned by him. The lack of agreement among investigators as to how digitalis affects the hearts of human beings with cardiac decompensation was due to the fact that the cardiac output was considered as the primary criterion of response. It is probable that both the investigators[18] who claimed that there is no increase in stroke output and those[19] who claimed that there is an increase in stroke output when decompensated hearts are digitalized were correct, and, had mechanical efficiency been calculated, they would have arrived at uniform conclusions.

The preceding studies on the mechanism of heart failure and the action of digitalis in restoring mechanical efficiency to optimal levels prompted us to study the action of digitalis on people with compensated organic heart disease. Because of the fact that cardiac enlargement is usually present in this group, it seemed probable that these hearts maintained their compensation at an increased total energy expenditure, or, in other words, functioned with a decreased mechanical efficiency. Consequently, it was conceivable that digitalis might be beneficial.

For this study we chose thirty-nine patients who had objective manifestations of organic heart disease of various types,* but who had never had evidence of congestive heart failure, such as dyspnea, orthopnea, congestion of the lungs, engorged liver, accumulation of fluid in the thoracic or abdominal cavity, or peripheral edema. The hearts varied in size from 0 to 40 per cent greater than the average normal heart, as calculated from the tables of Ungerleider and Clark.[20] All of these patients could be classified in Group 1 or Group 2A, as defined in *Criteria for the Classification and Diagnosis of Heart Disease.* These patients had normal venous pressures and circulation times. Their vital capacities were also measured, but patients with vital capacities lower than their predicted normal were not excluded if the results of other tests were normal, because this test, to a certain extent, is subjective, and the vital capacity may be changed by factors other than left ventricular failure. It is interesting that only four of these thirty-nine patients had vital capacities lower than 20 per cent of their predicted value, and in these cases there was no significant increase in vital capacity after digitalization, which would seem to show that the low vital capacities were due to factors other than passive congestion of the lung.

Circulation times were measured by injecting 3 c.c. of a 20 per cent solution of neocalglucon into the antecubital vein of the arm, held at the

*There were nine cases of rheumatic heart disease, twenty cases of hypertensive heart disease, and ten cases of coronary arteriosclerosis.

of heart function were made, were taken within five minutes of each other. In Fig. 1, the scatter of duplicate values for the efficiency index is plotted. The points fall about the 45 degree line at random, and the extreme limits of variation are 18 units. Approximately as many points fall above as below the 45 degree line, and since the average of duplicate measurements was taken as the value for the efficiency index, the extremes of variation were reduced by $\frac{1}{\sqrt{2}}$, or to 12.6 units.

In Fig. 2, this zone of variability in method is plotted as a percentage variation to conform with the method of recording the results in percentage changes from the original values. This zone includes the extremes of variation in about 130 measurements. Values falling outside the zone indicate a positive or negative change from their original state, whereas values falling within the zone cannot be considered to indicate a significant change from the original values. It is apparent that a more exact statistical analysis was not necessary, for the results are clear cut.

For the purpose of constructing a graph to demonstrate the relative individual and mean change in the efficiency index, we selected that efficiency index which had the largest value, whether it occurred in the first or the third week of digitalization. We believe that this is justified, for the maximal response to therapy should occur with the best digitalizing level. Since average doses of lanatoside C had to be used for all the subjects because there was no objective way of ascertaining the optimal dose for any one person, and since there are undoubtedly variations in the optimal requirements for digitalis from person to person, one is not justified in setting either the first or the third week as the time of best degree of digitalization for all patients, or in assuming that the degree of digitalization will be the same in the first week as in the third week. Furthermore, there was no way of telling whether the patients actually followed instructions regarding dosage, because they were all ambulatory and were not seen between measurements. It is to be emphasized, however, that had the results of either the first or the third week's observations been uniformly recorded, the conclusions, as well as the magnitude and the direction of changes, would not have been altered in any significant way.

Fig. 2 shows the scatter of the relative individual and mean changes in the efficiency index from the original values, represented by the 0 per cent line in each case, when patients with compensated heart disease and when normal persons were digitalized as described. It will be noted that the efficiency index in only five of the thirty-nine cases (10 per cent) did not show an increase after digitalization. These five observations fell within the zone of variability of the method. The efficiency index of the fourteen normal hearts decreased. Analysis of this figure would seem to justify the statement that lanatoside C will increase the mechanical efficiency of the hearts of most patients with organic heart disease that are not as yet demonstrably decompensated, whereas it will de-

and blood pressure to normal pre-exercise levels within two minutes after the exercise has been completed. The patient was instructed to walk over the platform so that the calculated number of ascents was completed in one minute. One minute after completion of the exercise, roentgenkymograms were made. Blood pressure readings were taken before and after the roentgenkymograms were made. This is a rather crude test for exercise tolerance, but it served the purpose of pointing out trends in the circulatory function of the normal and compensated heart before and after the administration of digitalis.

Upon completion of these preliminary studies, the patients were given lanatoside C and instructed to take six 0.5 mg.* tablets daily for two days, and then to take one and two tablets on alternate days as a maintenance dose. They were given no further instructions and in no way were cautioned to change or restrict their activities. The patients returned one week and three weeks after the preliminary observations and the beginning of digitalization. At each of these visits the patient reported at the same time and under similar conditions as on the original visit. The same routine was followed; duplicate kymograms were made at rest, and one kymogram was made after exercise. Between the second and third observations, electrocardiograms were made in all cases and compared with the original tracings to ascertain the effect of digitalis. Eighty per cent of the subjects with abnormal hearts and 65 per cent of those with normal hearts showed electrocardiographic evidence of digitalization. At the completion of the third observation, the venous pressure, vital capacity, and circulation time were rechecked and compared with the values obtained before digitalization.

Similar procedures and observations were carried out on the fourteen normal subjects. However, only two series of observations were made because it seemed inadvisable to maintain these persons on digitalizing doses for longer periods of time. The second series of observations was made one week after digitalization, and in exactly the same manner and under the same conditions as in the group with organic heart disease.

The administration of lanatoside C was discontinued at the completion of these observations, and the patients with compensated heart disease were followed in the cardiac clinic at the Minneapolis General Hospital. Approximately six months after the administration of lanatoside C had been discontinued, eighteen of the patients were recalled and roentgenkymographic studies of their heart function were repeated, using the same routine and technique as employed in the original studies. At this time only one series of duplicate observations was made, and the patients were given no digitalis. The purpose in re-examining these patients was to confirm or invalidate the observations made on the patients with compensated heart disease when they were digitalized.

Before presenting the results of our observations, it is necessary to show some measure of the inherent variability in the method. In all our studies, duplicate roentgenkymograms, from which the calculations

*A few small, asthenic patients were given five 0.5 mg. tablets, instead of six.

crease the mechanical efficiency of a normal heart. In other words, glycosides of digitalis are toxic for normal hearts but are beneficial to most abnormal hearts.

It is necessary to say a few words about the five cases in which there was no increase in the efficiency index, but in which the change in efficiency index lay within the zone of variability of the method. The one patient who had a decrease of 5 per cent was thirty-six years of age, and had a blood pressure of 140/90, and a 13 per cent enlargement of the transverse diameter of his heart. He was included in this series because he had a history of anginal distress. The results of physical examination were negative and the electrocardiogram was normal. As the patient was followed, it was found that his so-called anginal distress was associated with attacks of ventricular paroxysmal tachycardia. The degree of organic heart disease was in all probability minimal, so that one might expect him to respond more like the patients with normal hearts. Of the four other patients, one was a young man, 21 years old, with a recently discovered aortic stenosis and insufficiency which were asymptomatic. The other three patients had been coming to the out-patient department of the hospital for a long time. One had coronary arteriosclerosis, another had rheumatic heart disease, and the third had hypertensive heart disease. Electrocardiograms of these patients showed no digitalis effect. Whether this means that they did not take the digitalis as directed, it is not possible to know. It is also noteworthy that all five of these patients had circulation times that were less than sixteen seconds.

The wide scatter of improvement in the efficiency index in the thirty-four cases was probably associated with varying gradations of myocardial insufficiency in this group, as yet not severe enough to produce frank symptoms and signs of cardiac failure. The normal hearts responded to digitalization with a mean decrease in efficiency of 33 per cent. The normal hearts were closely grouped, probably because the function of each heart was very similar to that of every other, and therefore the action of digitalis could be expected to produce similar results.

Fig. 3 shows the response of normal and abnormal hearts to the graded exercise tests. Before digitalization both the normal and abnormal hearts responded with an increase in the efficiency index of between 5 and 6 per cent. This observation on the human heart is in accord with the laboratory observations of Starling and Visscher,[7] who noted that the heart of the dog responded with a slight increase in mechanical efficiency when an increased load was placed on it. After digitalization, twenty-two patients with abnormal hearts responded to exercise with a mean increase in efficiency index of 29 per cent above the resting level, or 23 per cent above the efficiency index before the administration of digitalis. The normal group, on the other hand, showed a mean decrease in efficiency index of 25 per cent below the original resting values, or 30 per cent below the efficiency index before the administration of digitalis. We can therefore say that the response of compensated and

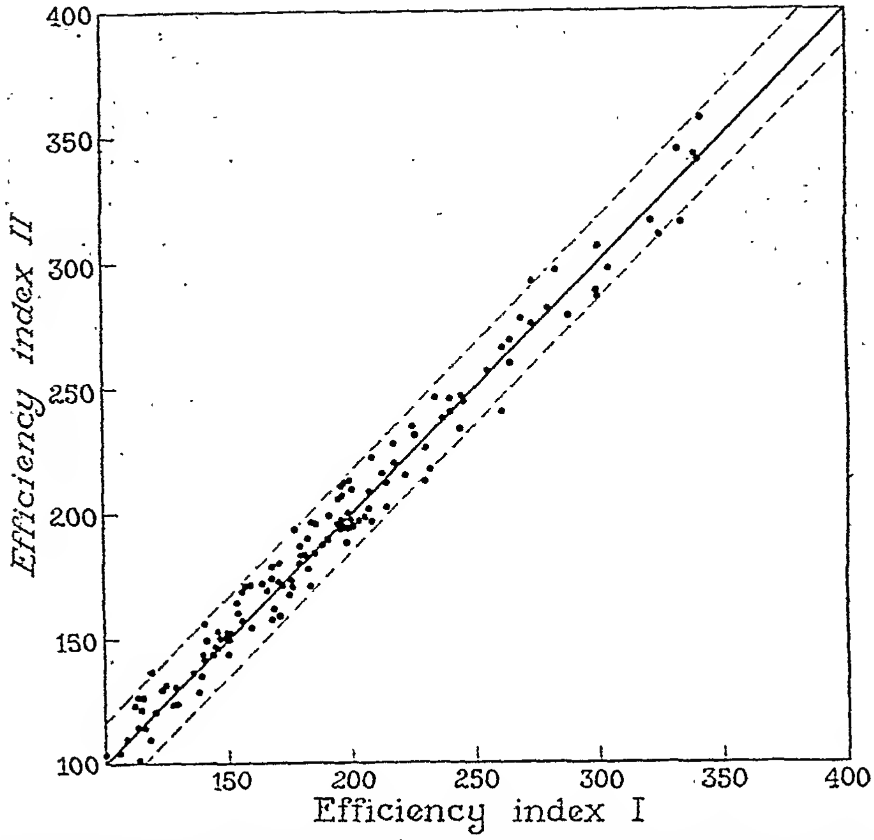

Fig. 1.—Scattergraph demonstrating the variation in duplicate measurements of the efficiency index when efficiency index I is plotted against efficiency index II.

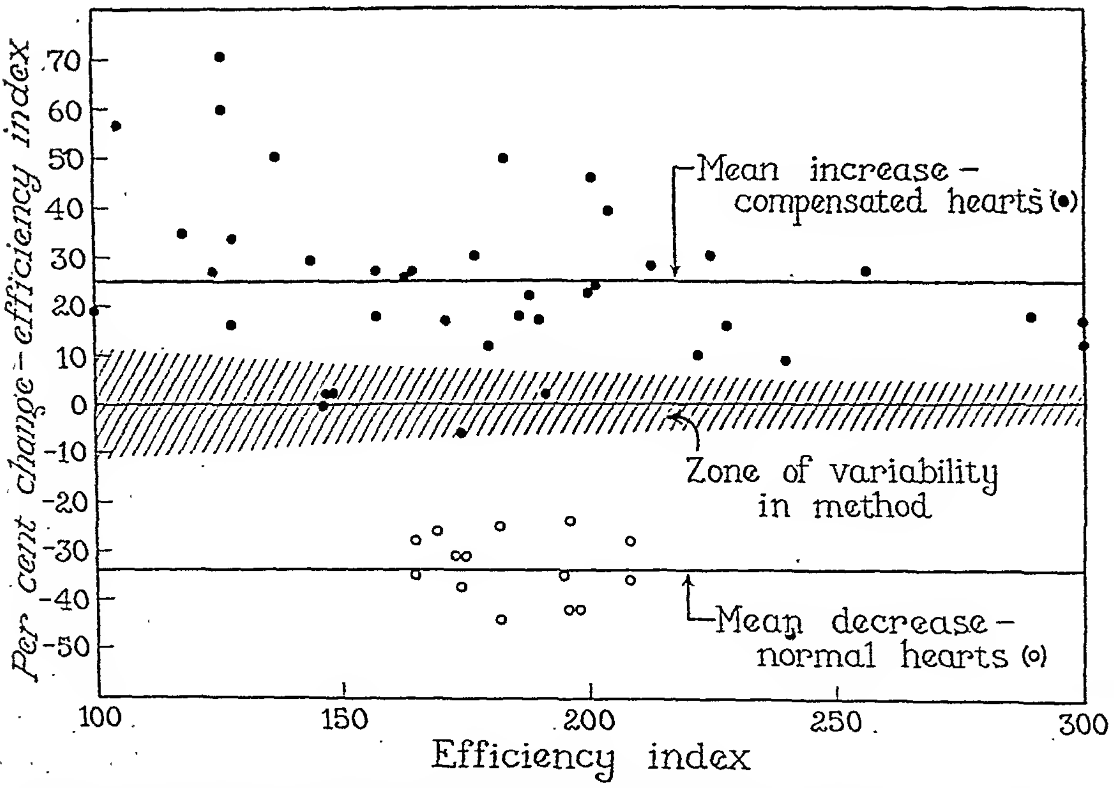

Fig. 2.—Scattergraph demonstrating the relative individual and mean change in efficiency index from original values (represented by 0 per cent line in each individual) when normal subjects and patients with compensated heart disease were digitalized.

by the decrease in the efficiency index below the zone of variability of the method.

The degree of improvement in the efficiency index of the abnormal hearts was found to bear no direct relation to the size of the heart. The increase in efficiency index seemed to bear very little relationship to the type of heart disease. The mean increase in efficiency index was as follows: 22 per cent in the cases of hypertensive heart disease, 26 per cent in the cases of rheumatic heart disease, and 27 per cent in the cases of coronary arteriosclerosis. These differences in response among the types of heart disease are not significant, although there seems to be a tendency toward greatest benefit in the cases of coronary arteriosclerosis. We frequently have noticed that digitalis seems to be especially efficient in cases in which heart failure is associated with coronary arteriosclerosis. It is the limitation in oxygen supply which ultimately brings about failure in this group of cases, and it seems probable that digitalis would produce the most favorable results in this group by causing more efficient utilization of the available supply of oxygen.

There is a rough correlation between the ratio of stroke output to diastolic volume and the response to digitalis, so that the more disproportionate the stroke output to the diastolic volume, the better the response to digitalis. Likewise, this ratio segregates the normal from the abnormal heart (Fig. 3). Consequently, the ratio is valuable as a rough index of cardiac fitness, and one can say that the more disproportionate the stroke output to the diastolic volume, the less effective is the heart as a pump.

The mean change in efficiency index in the twelve cases in which the circulation time was between sixteen and twenty seconds was 39.9 per cent, whereas the mean change in efficiency index in twenty-six cases in which the circulation time was less than sixteen seconds was only 18.3 per cent. Seven of the eight patients who had an increase in their efficiency index of 35 per cent, or more, had a circulation time of between sixteen and twenty seconds. All five of the patients who fell within the zone of variability, and, consequently, showed no significant response to digitalis, belonged in the group with circulation times of less than sixteen seconds. This would seem to indicate that an increase in the circulation time appears rather early in the development of heart failure. It also would seem to indicate that one may expect a good increase in the mechanical efficiency of organically diseased hearts if digitalis is given, despite the absence of the usual signs and symptoms of frank heart failure, providing the circulation time is between sixteen and twenty seconds.

Since the efficiency index is an expression of work per beat divided by the diastolic volume, and since the work per beat is obtained by multiplying the stroke output by the mean arterial pressure, it is obvious that any one of these functions, considered by itself, is insufficient to explain the whole story of the function of the heart and its response to digitalis therapy. In Fig. 5 we have plotted the scatter of relative individual

organically diseased hearts to increased strain is definitely improved by digitalis, whereas the response of normal hearts is definitely impaired by digitalis.

The change in the efficiency index caused by digitalis was of approximately the same magnitude in this series as at rest, namely, +23 per cent and –30 per cent, respectively, for abnormal and normal hearts, as contrasted with +24 per cent and –33 per cent, respectively, at rest. This degree of correlation in the magnitude and direction of response of normal and abnormal hearts to digitalis under both conditions of rest and exercise seems striking.

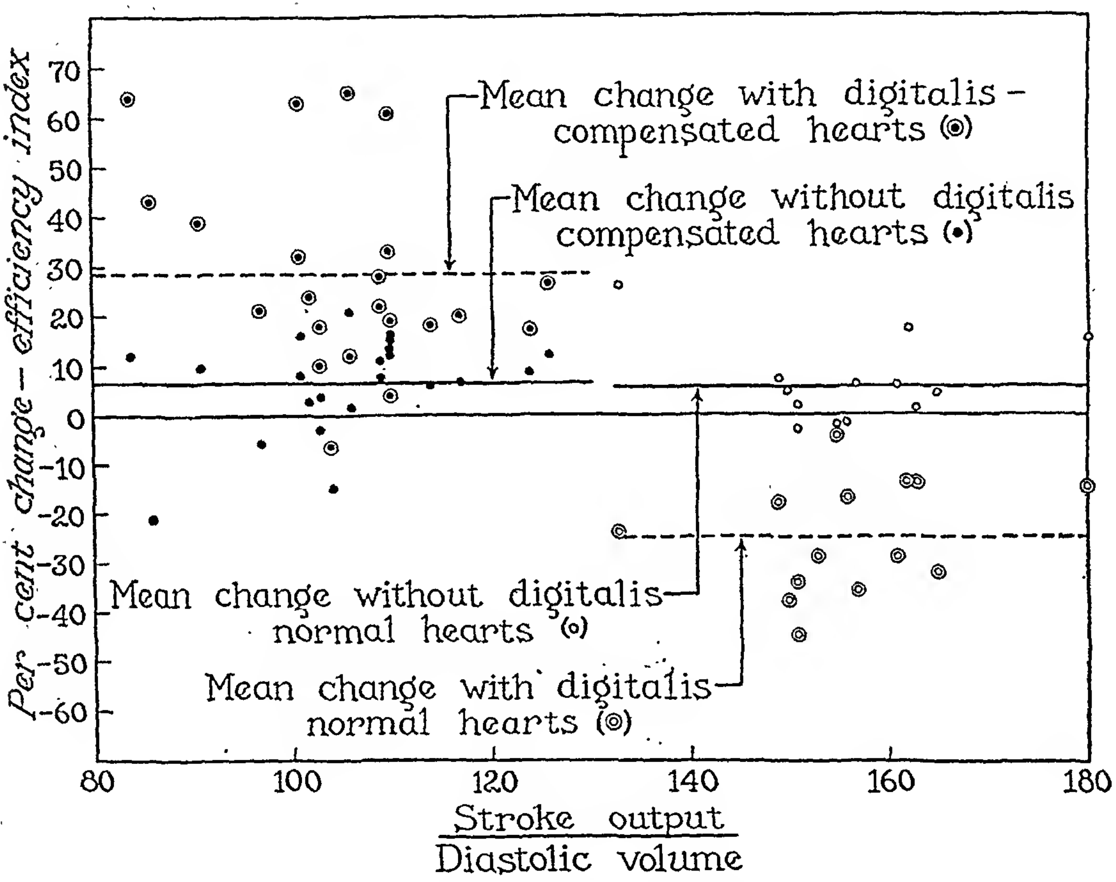

Fig. 3.—Scattergraph demonstrating the relative individual and mean change in efficiency index from original values in normal subjects and in cases of compensated heart disease caused by exercise, before digitalization and after digitalization. The changes in efficiency index are plotted against the ratio of $\frac{\text{stroke output}}{\text{diastolic volume}}$ which is a rough index of heart fitness.

Measurements of cardiac function were again made six months after the administration of digitalis had been discontinued. Fig. 4 shows the results in the eighteen cases that were restudied. Whereas the mean percentage increase in the efficiency index was 32 per cent for this group when digitalized, the mean percentage change in efficiency index was –7 per cent six months after the administration of digitalis had been discontinued. From these studies it is apparent that these patients were no better off six months after the administration of digitalis had been discontinued than they were before it was started. In nine cases (50 per cent) the function of the heart was definitely worse, as indicated

and mean changes in stroke output from original values, represented by the 0 per cent line, when patients with compensated heart disease, and when normal persons, were digitalized. The abscissas represent the original values, and the ordinates represent the percentage change in stroke output after digitalization. As in the case of the efficiency index, the maximal variation in the method of measuring the stroke output was ascertained by making a scattergraph of duplicate measurements of stroke output. All of the points are closely grouped about the 45 degree line, and have a maximal variation of 4.1 units. The zone of maximal variation in the method has been drawn in Fig. 5 as a percentage variation, to conform with the method of reporting changes in stroke output. Again a sharp difference between the response of the compensated hearts and that of the normal hearts is demonstrated. There was a mean increase of 19.4 per cent in the stroke output of the compensated hearts, whereas the normal hearts showed a mean decrease of 34.6 per cent. Twenty-nine (75 per cent) of the patients with compensated heart disease fell above the zone of variability in the method, and showed a definite increase in stroke output. The remaining ten patients (25 per cent) showed no significant change in stroke output. All of the normal subjects fell below the zone of variability in the method, and showed a significant decrease in stroke output. These observations are in accord with those of Stewart and his co-workers,[6] in that not all patients with compensated heart disease respond to digitalis with an increase in stroke output; some show no significant change. One must remember that changes in the stroke output cannot be relied on to give a complete picture of functional change in the heart after digitalization. It is necessary to know the change in blood pressure, because this is one of the factors in mechanical work, as well as the change in diastolic volume, which is a measure of total energy metabolism.

It will be noted that the original stroke output in the cases of compensated heart disease was of the same order as the original stroke output in the normal group, and it may seem perplexing that there was a marked increase in stroke output after digitalization. However, it is to be remembered that the stroke output in this compensated group was small compared with the size of the heart. In consequence of the increased diastolic volume, these compensated hearts developed more total energy per stroke than normal hearts; therefore, when enlarged hearts increase their mechanical efficiency, they will expel much more blood per beat than the normal heart if the diastolic volume remains approximately the same. Digitalis, by increasing the mechanical efficiency of these organically diseased hearts, converts more of the available energy to useful work, and if the diastolic volume remains larger than normal, it will produce an increase in stroke output. The decrease in the stroke output of the normal hearts is in accord with observations of other investigators, who noted a decrease in the stroke output of normal hearts[6, 17, 24, 25] of human beings and dogs when digitalis was given.[26-28]

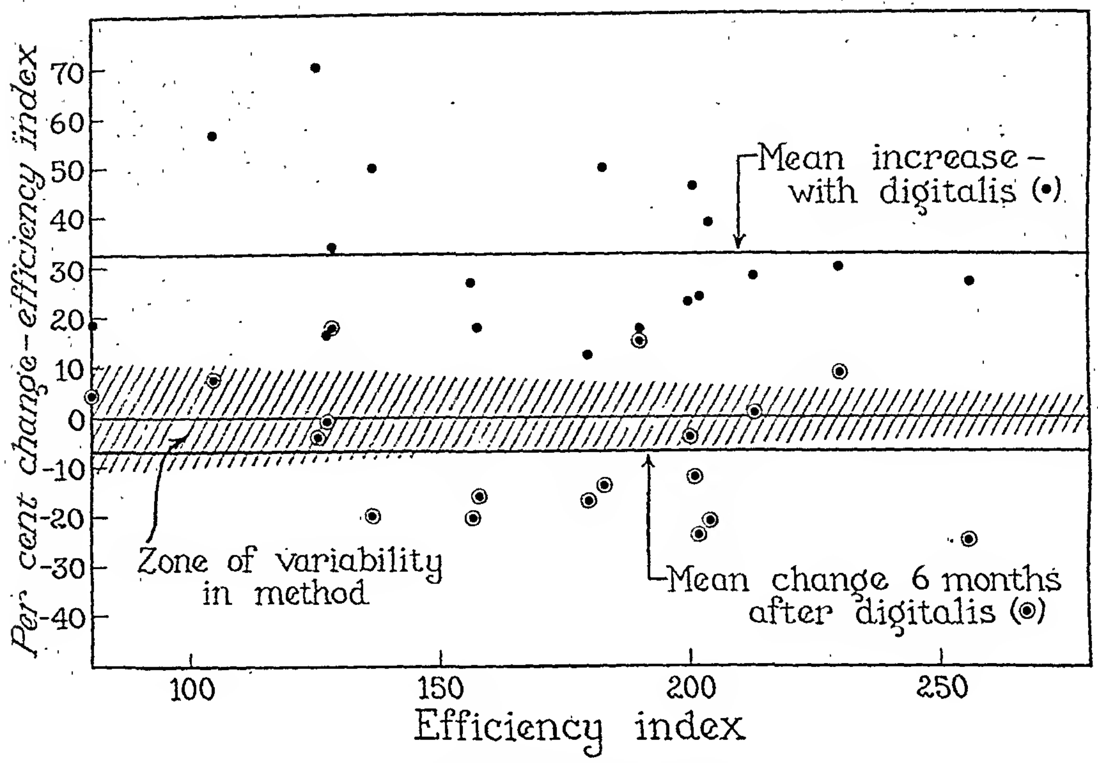

Fig. 4.—Scattergraph demonstrating the relative individual and mean change in efficiency index from original values in cases of compensated heart disease during period of digitalization and six months after administration of digitalis had been discontinued.

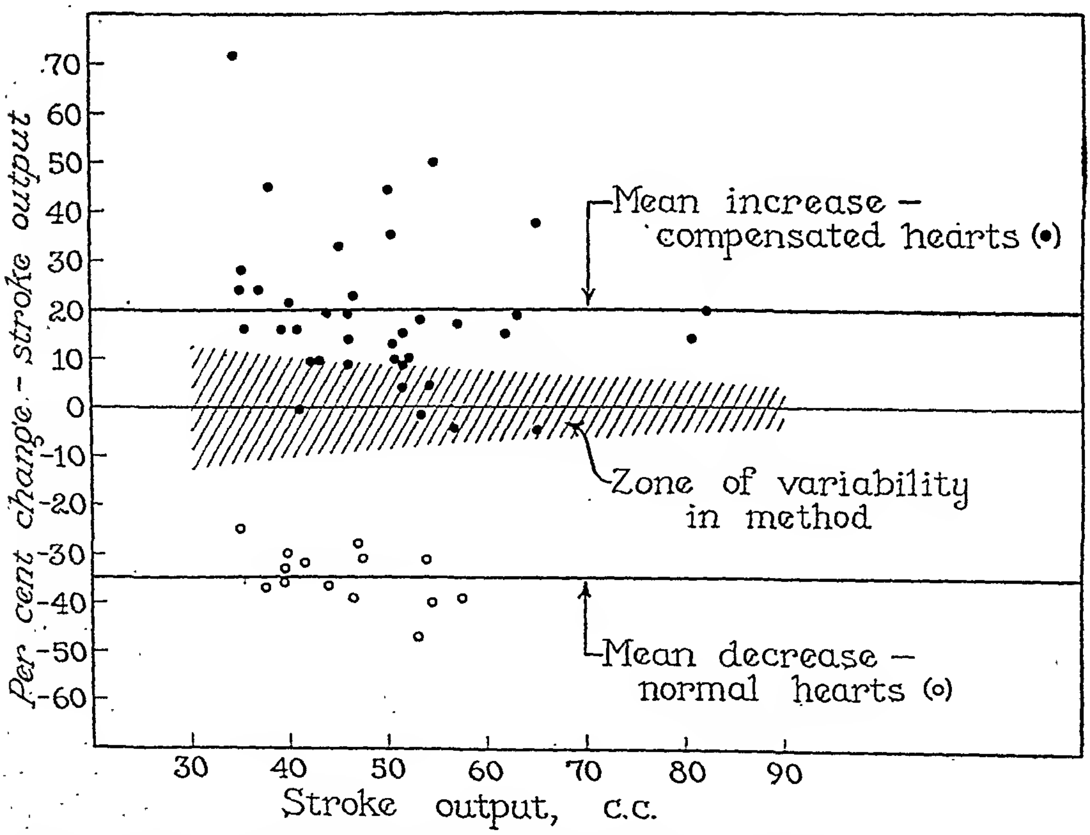

Fig. 5.—Scattergraph demonstrating the relative individual and mean change in stroke output from original values when normal subjects and patients with compensated heart disease were digitalized.

tion. This difference in the trends of the systolic volume of the abnormal and normal hearts after digitalization gives a clue to the mechanism by which digitalis decreases the stroke output of the normal heart and increases the stroke output of the abnormal heart.

Our observations show that, in cases in which the heart is normal, digitalis, when given in full, digitalizing doses, acts as a myocardial poison, so that the mechanical efficiency is reduced, and, therefore, the percentage of energy converted to circulatory work is decreased Inasmuch as the heart is incapable of performing as much circulatory work as it did previous to digitalization, it empties itself less completely, and, as a consequence, the systolic volume is increased and the stroke output decreased. On the other hand, in abnormal hearts a greater percentage of the available energy is converted into circulatory work, with a resultant increase in the force of systolic contraction. As a consequence, the systolic volume decreases and the stroke output increases.

The circulation time, venous pressure, and vital capacity were remeasured during the administration of digitalis. No significant changes were noted in the venous pressures, which were all within normal limits to begin with. In ten cases, the circulation time was between seventeen and twenty seconds; in eight of these cases the circulation time was less than sixteen seconds after digitalization, which is readily explained by the increase in stroke output. In all cases there was a mean increase in vital capacity of only 2 per cent after digitalization. In only two of the twenty cases in which the vital capacity was less than the predicted normal did the capacity increase to the predicted normal after the administration of lanatoside C. In the remaining cases there was either no change or a minimal decrease in vital capacity. From these observations it seems apparent that the initial reduction of vital capacity in these cases was caused by extracardiac factors.

Subjectively, the majority of the patients with compensated heart disease noted no change while digitalis was being administered. A few patients stated that physical exertion did not exhaust them as rapidly as it previously had. One patient stated that she had difficulty "catching her breath" during the first week of digitalization, but this symptom subsequently disappeared. This patient was a woman, aged 22 years, with a recently discovered aortic stenosis and insufficiency. She had an increase in her efficiency index of only 2 per cent when she was digitalized; therefore, she showed neither a positive nor a negative response to digitalization.

CONCLUSIONS

1. Of thirty-nine patients with clinically compensated, but organically diseased, hearts, thirty-four (87 per cent) showed definite improvement in mechanical efficiency when they were digitalized, whereas the remaining five, although they did not show any significant improvement, were, nonetheless, no worse after digitalization.

Both the normal and abnormal hearts showed a decrease in the diastolic volume when digitalized; the mean percentage decrease was 3.2 per cent in the normal group and 3.8 per cent in the abnormal group,

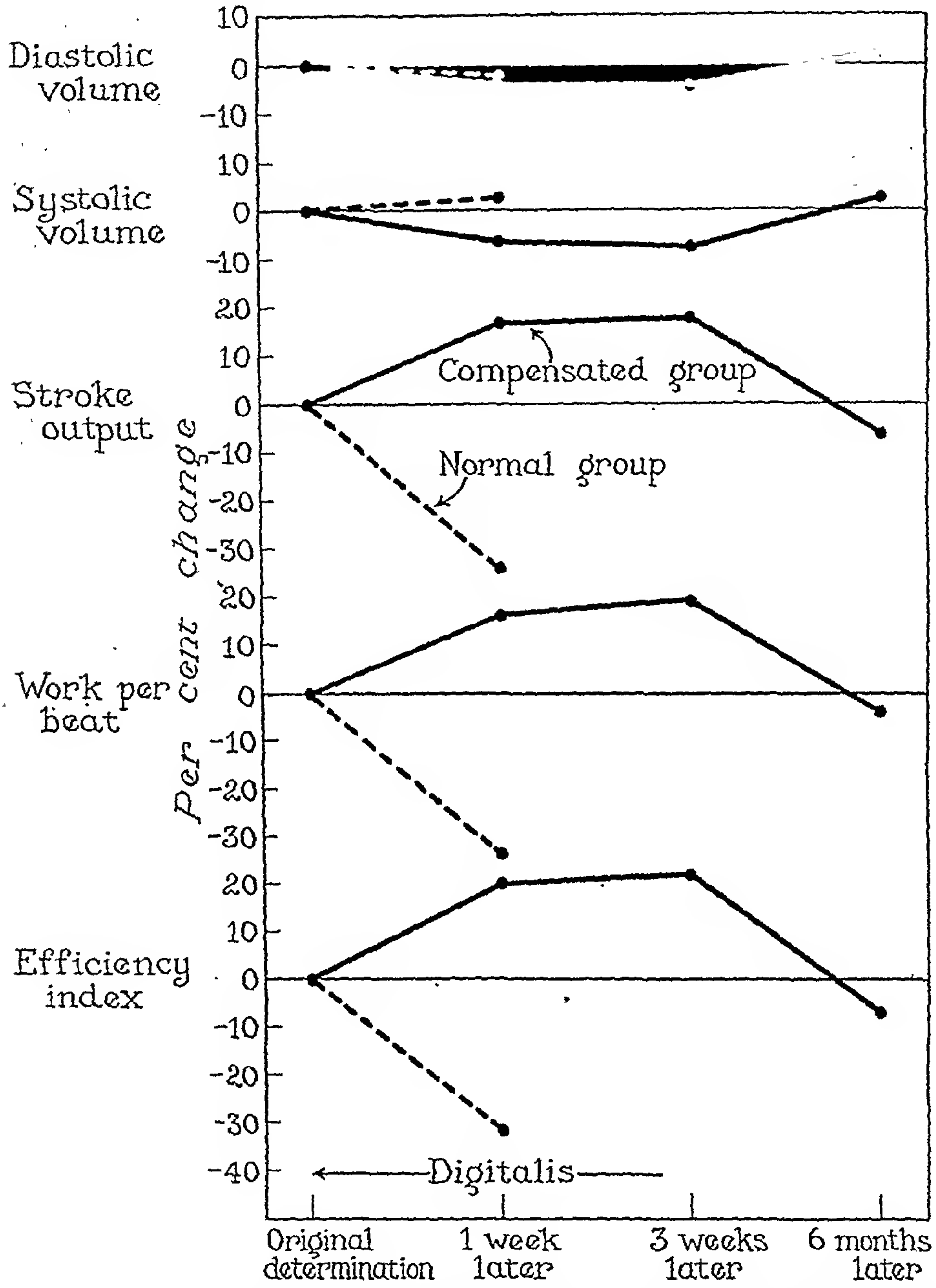

Fig. 6.—Diagram demonstrating the mean relative change in the various heart functions from original values in normal subjects and in cases of compensated heart disease during the period of digitalization. In the latter group the mean relative changes that occurred six months after the administration of digitalis had been discontinued have also been charted.

as shown in Fig. 6. In other words, the total consumption of oxygen (liberation of energy) was reduced slightly in both groups. Six months after the administration of digitalis had been discontinued, the diastolic volume of the abnormal hearts had increased slightly beyond the original volume. One will note in Fig. 6 that the systolic volume of the abnormal hearts decreased even more than did the diastolic volume, whereas the systolic volume of the normal hearts increased after digitaliza-

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2. On the other hand, fourteen persons with normal hearts showed a definite impairment in cardiac function after the administration of digitalis. In these cases digitalis acted as a cardiac poison.

3. Of the eighteen patients with compensated, but organically diseased, hearts who were restudied six months after digitalization was discontinued, nine had the same cardiac function that they had before digitalization; in the remaining cases, the heart was less efficient than it had been before digitalization.

4. The degree of improvement in mechanical efficiency in cases of compensated heart disease has been correlated with circulation time. It was greatest in cases in which the circulation time was sixteen to twenty seconds.

5. The response to digitalis was essentially the same in hypertensive and rheumatic heart disease and in coronary sclerosis.

6. Digitalis exerts its action primarily on the cardiac muscle by changing the mechanical efficiency of the heart.

a. In the compensated organically diseased heart it increases the mechanical efficiency, so that a greater percentage of the total energy liberated is converted to mechanical work.

b. In the normal heart, digitalis acts as a poison and decreases the mechanical efficiency, so that a smaller percentage of the total energy liberated is converted to mechanical work.

7. It appears that every heart is endowed with the ability to work at a given mechanical efficiency which cannot be increased by digitalis unless organic heart disease has reduced this inherent mechanical efficiency, under which circumstances digitalis tends to raise mechanical efficiency toward normal levels.

8. We believe that digitalis is definitely indicated for organically diseased and enlarged hearts which appear compensated, when the circulation time, as measured by the calcium gluconate arm-to-mouth method, is greater than sixteen seconds.

9. Our studies seem to indicate that digitalis does no harm and is beneficial for many of these hearts when the circulation time is less than sixteen seconds, but since the main objective in digitalizing these patients is to increase life expectancy and physical fitness and to ward off heart failure, a long period of observation will be necessary to ascertain the ultimate benefit of digitalis.

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k and r^2 are the same for the three points, they may be disregarded. Irrespective of what the actual value of angle θ is, the sum of cos θ + cos (θ + 120°) + cos (θ + 240°) always equals zero. For example, in Fig. 1, *a,* the value of angle θ is approximately 90°. The potentials of the extremities would therefore be:

LA = cos 90° = 0
RA = cos 210° = cos − 30° = −.87
LL = cos 330° = cos + 30° = +.87
and 0 + .87 + (−.87) = 0.

2. Any two points (on the same plane of the sphere) separated by an angle of 180° will have potentials of the same magnitude but of opposite polarity. An example will make this clear:

In Fig. 1, *b,* the potentials of points *A* and *B* are as follows:

A = cos θ
B = cos (180° − θ).
Since θ is 120°, 180° − θ is 60°. The cos 60° is ½; and cos 120° is −½.

3. Since the magnitude of the potential of any point (on the periphery of the sphere) varies with the cosine of the angle formed by a line drawn from the point to the center of the dipole and its positive pole, there will be two points of equal maximum potential, but of opposite polarity. These, of necessity, will be located so that they make angles of 0° and 180°, respectively, with the dipole.

4. Since this is so, the following indirect method can be used to find these two points of maximum potential: If any point, *P,* be taken on the surface of the sphere (lying on the same plane as *RA, LA,* and *LL*), and if the potential difference between *P* and every other point on the surface of the sphere in this plane be ascertained (as with the electrocardiograph), the largest (+) deflection, *irrespective of its actual value,* and the deepest (−) deflection, *irrespective of its actual value,* will be derived from the two points of equal maximum potential but of opposite polarity. Fig. 1, *c,* illustrates this. Assume that *P* has a potential of −2 units. If *P* and *G* are connected to the electrocardiograph and the potential difference measured, it will be found to be +5.6 (−2 − [−7.6]). Similarly, *P* − *H* = +8, *P* − *I* = +4.7, *P* − *J* = −2, *P* − *K* = −9.6, *P* − *L* = −12, *P* − *M* = −8.7, and *P* − *N* = −2. The maximum (+) value is +8, formed by the potential difference between *P* and *H*. The maximum (−) value is −12, formed by the potential difference between *P* and *L*. The actual values of points *H* and *L,* as can be seen in Fig. 1, *b,* are −10 and +10, respectively.

5. As a final corollary, it should be emphasized that, according to the Einthoven concept, the dipole and the extremities lie on the same plane (the frontal plane of the body, which divides the body into anterior and posterior portions). Consequently, the potentials of any vector passing in a direction at right angles to the frontal plane (i.e., anteriorly

THE VALIDITY OF THE EINTHOVEN TRIANGLE HYPOTHESIS

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INTRODUCTION

In RECENT work of ours, the technique and principles of augmented unipolar extremity leads were described.[1, 2, 3] Inasmuch as the use of this technique, just as with Wilson's ordinary unipolar extremity leads,[4] depends on the validity of the Einthoven triangle hypothesis, it was deemed advisable to review this latter subject and re-evaluate it, if possible.

In its barest outline, the Einthoven hypothesis may be described as follows: (1) The body is a homogeneous conducting medium.[9] Whether its shape be considered as a triangle, a circular disk, an infinite lamina, or a sphere of large or infinite radius is unimportant.[5] In this paper, it shall be considered as a sphere. (2) The electrical activity of the heart, at a given instant, may be regarded as a dipole (a + and − pole, separated by a finite distance). (3) The dipole is located in the center of the sphere. (4) The extremities (right upper, left upper, and left lower) may be considered as linear extensions of three points on the periphery of the sphere. They lie on the same plane as the dipole (corresponding to the frontal plane of the body), and are so located that, if they were to be joined by straight lines, they would form the apices of an equilateral triangle, in the center of which would be the dipole. This, in essence, is the Einthoven triangle concept.*

If this is so, certain corollaries may be deduced:

1. The algebraic sum of the potentials of the extremities, at a given instant, must equal zero. This is illustrated in Fig. 1, *a*. In Fig. 1, *a*, if the vector (the arrow) indicates the magnitude and direction of the electrical activity of the heart at a given instant, the potential at the left arm (*LA*) is equal to $\frac{K \cos \theta}{r^2}$, where k is a constant, r the distance of the electrode to the center of the dipole, and θ the angle made by a line drawn from LA to the center of the dipole and the (+) pole of the vector. The potential at *RA* is therefore $\frac{K \cos (\theta + 120°)}{r^2}$, and the potential at the left leg (*LL*) $\frac{K \cos (\theta + 240°)}{r^2}$. Since the values of

Work done under a Fellowship of the Martha M. Hall Foundation.

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Received for publication June 2, 1944.

*The Einthoven equation, Lead II = Lead I + Lead III does *not*, however, depend on the validity of the above concept[6] (see Appendix).

point on the frontal plane of the body. As a rule, we placed the wandering electrode in the right axilla, in the right supraclavicular fossa, on the head (the electrode was arbitrarily placed at the angle of the right jaw, inasmuch as all points on the head have practically the same potential[7]) in the left supraclavicular fossa, on the left arm (Lead I), in the left axilla, at the left midaxillary line at successive points, beginning at the level of the fourth intercostal space anteriorly and proceeding to the lower level of the ribs; on the left leg (Lead II), and at varying points along the right midaxillary line.

The records taken with the wandering electrode at each of these points recorded the difference of potential between the potential of the right arm (the fixed point) and the potential of any of the points just described. With these records the electrocardiograph was standardized so that a deflection of 1 cm. represented a potential of 1 millivolt. After the records were taken, they were immediately developed and studied.

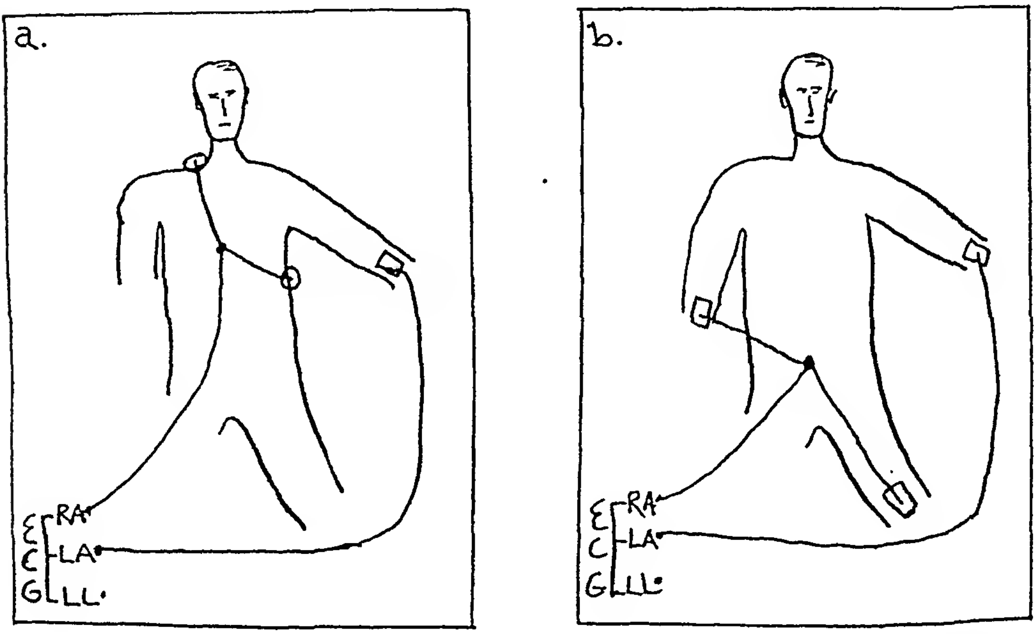

Fig. 2.—*a*, Hookup to take a record from the left arm, using as an indifferent electrode two points of maximum potential (as ascertained by the method described in the text). *b*, Hookup to take a record from the left arm, using the author's method of obtaining augmented unipolar extremity leads.

The points from which the largest (+) deflection (irrespective of its actual value), and the deepest (–) deflection (irrespective of its actual value) were thereby obtained. Electrodes were reapplied to these two regions and connected together by means of an ordinary copper wire shunt (Fig. 2, *a*). These joined electrodes were then used as an indifferent electrode, and records were taken from the right arm, left arm, and left leg (Figs. 3 and 4). In these records, the electrocardiograph was so standardized that a deflection of 1.5 cm. was equivalent to a potential of 1 millivolt. After this was done, the unipolar extremity records were taken from the right arm, left arm, and left leg, using the author's technique of obtaining augmented unipolar extremity leads.[1] With this method the records obtained are three-halves of their actual magnitude, even when the electrocardiograph is standardized in the usual manner. The augmented unipolar extremity lead records were then com-

or posteriorly) will be without effect on any point on the frontal plane, including the extremities. The reason for this is that all points on the frontal plane form an angle of 90° with such a vector (and $\cos 90° = 0$) (Fig. 1, *d* and *e*).

The use of the indifferent electrode of zero potential, employed by the author to obtain unipolar leads, depends on the validity of corollary 1, namely, that the algebraic sum of the extremity potentials at any given instant equals zero. Similarly, if the points of maximum equal potential but of opposite polarity were to be found and joined together to a central terminal, the potential at this terminal would also be zero, according to Kirchkoff's Law.[1] (In Fig. 1, *c*, the value at such a terminal would be equal to $\frac{+10 - 10}{2} = 0$.) Therefore, electrocardiograms taken with either of these two methods should be identical if the postulates of the Einthoven concept are valid. It was this method that we used in the following study of the validity of the Einthoven hypothesis.

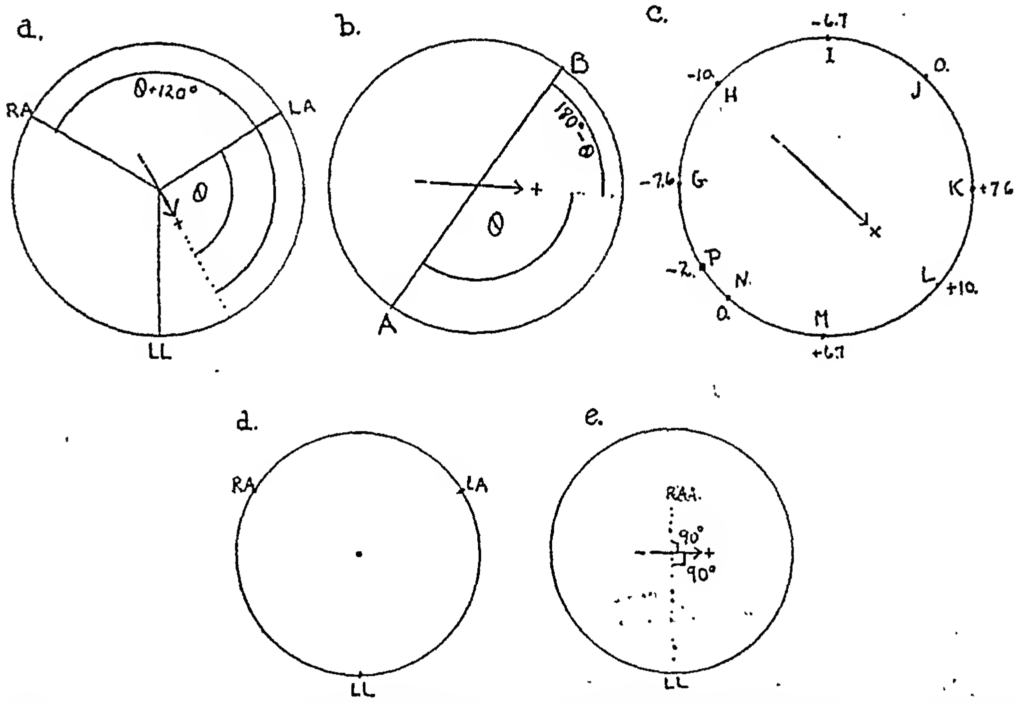

Fig. 1.—*a*, The relations of the extremities to the dipole representing the electrical activity in the heart. *RA*, right arm; *LA*, left arm; *LL*, left leg; the arrow represents a dipole. For further details see text. *b*, The relations of any two points separated by an angle of 180° to the dipole. For details see text. *c*, The potentials of varying points on the surface of the sphere lying on the same plane as the dipole. For details see text. *d*, and *e*, The effect of a dipole which points in a direction at right angles to the plane of the extremities. In *d*, the dipole may be considered as pointing inward, away from the reader. In *e*, the sphere is viewed from the right side. The full magnitude of the vector (the arrow) can now be seen. For further details see text.

METHOD

Our procedure was as follows: The subject either sat or reclined. The right arm was arbitrarily chosen as a fixed point. The electrocardiograph was set for Lead I. The right arm lead wire from the electrocardiograph was connected to the electrode on the right arm, and the left arm lead wire from the electrocardiograph was connected to another electrode which was placed on varying portions of the body (all lying on the frontal plane). It was not necessary to take records from every

pared to the extremity records which were taken with the two points of maximum (+) and (−) potential as the indifferent electrode.

MATERIAL

Ten cases, selected at random from patients in the hospital, were studied. Among these were five with normal electrocardiograms, three with the patterns of left ventricular preponderance, and two cases of myocardial infarction.

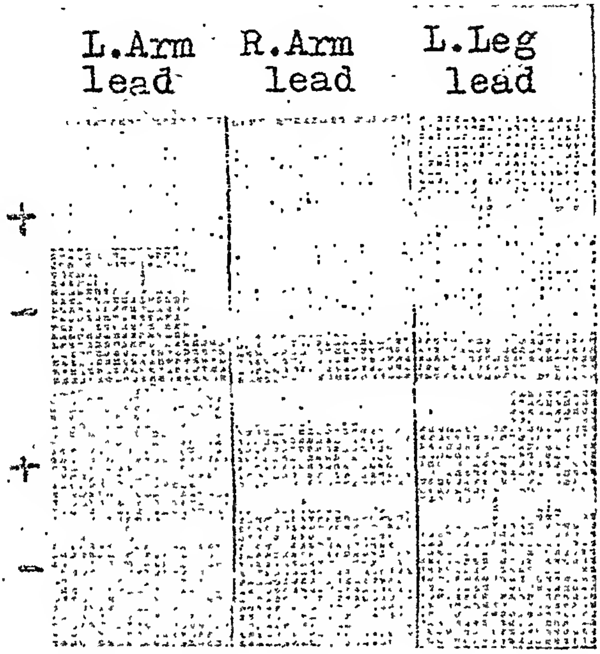

Fig. 4.—Case 2. Upper row, extremity leads obtained by using as an indifferent electrode two points on the body, namely, the right supraclavicular fossa and the left midaxillary line at the level of the sixth intercostal space anteriorly (these two points were determined by the method described in the text). Lower row, the augmented unipolar extremity leads.

RESULTS

Our technique was, at best, relatively crude, inasmuch as it is difficult at times to ascertain exactly the midaxillary line, and because slight variations in position, especially in the left midaxillary line near the heart, will sometimes cause considerable change in the potential. In spite of this, and the small number of subjects studied, the constancy of the results is significant. Figs. 3 and 4 show two examples. Case 1 was that of a 54-year-old white man who suffered from extensive myocardial infarction. The three standard leads had a downwardly directed QRS and low voltage, indicating the extensive myocardial damage.[8] In this case the distribution of polarity was just the opposite of that which is encountered ordinarily in either normal subjects or in cases of heart disease because here the largest (+) deflection was found in the right axilla (point *2,* Fig. 3), and the deepest (−) deflection was found in the left leg (point *11,* Fig. 3). (In the normal the right upper half of the body usually has a [−] potential and the left lower half of the

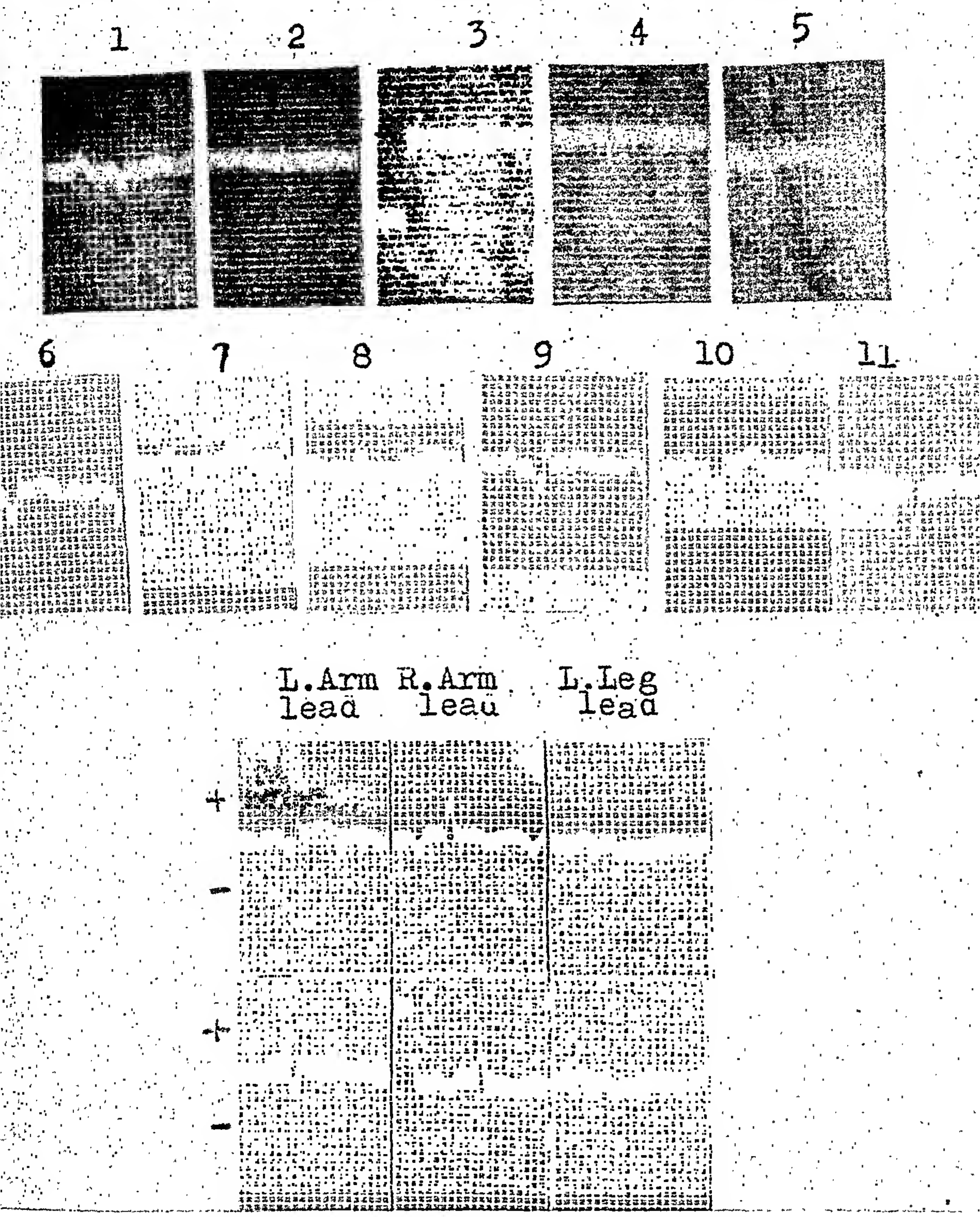

Fig. 3.—Case 1. Points *1* to *11* represent the electrocardiograms derived by using the connections of Lead I, but, instead of having the left arm lead wire on the left arm, placing it on various points, as follows: *1*, right midaxillary line at level of third intercostal space (anteriorly); *2*, right axilla; *3*, right supraclavicular fossa; *4*, head (electrode at the right angle of jaw); *5*, left supraclavicular fossa; *6*, Lead I (left arm); 7 to *10*, points along the left midaxillary line; *11*, Lead II (left leg). The upper row of extremity leads (left arm, right arm, and left leg leads) was obtained by connecting points *2* and *11* to form an indifferent electrode. These records were taken with the electrocardiogram at three-halves normal sensitivity. The lower row of extremity leads record the augmented unipolar extremity leads.

distant from each other or from the dipole. The mean potential of these two points may or may not equal zero. If zero, it will be either because the conditions of the Einthoven hypothesis exist, or as a fortuitous result.

Similarly, any three points, other than the extremities, may be selected and joined to a central terminal. The potential of this central terminal also may or may not equal zero. Its value will be zero either because the conditions of the Einthoven hypothesis exist, or fortuitously.

The mean potential of the points of maximum (+) and (−) potential and the mean potential of the three extremities can therefore equal each other as a consequence of only three conditions: 1. The Einthoven triangle hypothesis is invalid, and the equality of values is a matter of coincidence. 2. The Einthoven hypothesis is invalid, but such other conditions exist to cause the equality to be maintained. In such a case, the values of each would either be (+) or (−), and only zero fortuitously. 3. The Einthoven hypothesis is valid, and both values are zero.

With respect to the first condition, the equality of values may be the result of coincidence in an isolated case, but it is difficult to conceive of coincidence as a determining factor when more than one case is studied. With respect to the second condition, it might be possible to devise a theoretical system in which such a relationship would hold regularly, although we have not been able to do so. Therefore, it may be said that the equality of values is *not* due to construction, but is a manifestation of the validity of the Einthoven hypothesis.

It may be pointed out that it is not necessary to get the maximum values of the P and T waves (which vary independently of the QRS complex), because, as is demonstrated in corollary 2 and Fig. 1, *b*, *any* two points separated by an interval of 180° will record potentials equal in magnitude but opposite in polarity.

CONCLUSIONS

The use of the system of unipolar leads devised by Wilson and by the author depends on the proposition that the algebraic sum of the potentials of the extremities at a given instant always equals zero. This can only be so, however, if conditions within the body correspond to the postulates of the Einthoven triangle concept which were described in the text. However, direct proof of this is impossible because, irrespective of whether the hypothesis is valid or not, the algebraic sum of the extremity potentials, as obtained in the electrocardiogram, equal zero. This, as was pointed out, is a result of construction. However, if the Einthoven concept is valid, another corollary can be deduced, namely, that every two points on the surface of the body lying on the same plane as the source of electrical activity and separated by an angle of 180° have values equal in magnitude but opposite in polarity. By means of this corollary, the points of maximum equal potential, but of opposite polarity, can be obtained, theoretically and actually. Since the

body usually is [+].[7]) Notice how not only the character of the QRS complexes but of the RS-T segment deviations and T waves are identical.

Case 2 was that of a 62-year-old white man with moderate hypertension. In this instance the largest (+) deflection was found in the left midaxillary line at the level of the sixth intercostal space, and the deepest (−) potential in the right supraclavicular fossa. These two points were joined to form a central terminal, and the records shown in the upper row of Fig. 4 were then recorded. These are compared to the augmented unipolar extremity leads (Fig. 4, lower row).

DISCUSSION

One of the characteristics of unipolar extremity leads, as obtained by the author's method, is the fact that, even if the indifferent electrode does *not* have a potential of zero, the algebraic sum of the potentials of the records obtained from the three extremities will equal zero. This is merely due to construction. Thus, the right arm lead actually records the difference of potential between the right arm and the mean potential of the left arm and left leg, or $RA - \frac{LA + LL}{2}$. Similarly, the left arm lead records $LA - \frac{RA + LL}{2}$ and the left leg lead, $LL - \frac{RA + LA}{2}$. The sum of these three leads is

$$\left(RA - \frac{LA + LL}{2}\right) + \left(LA - \frac{RA + LL}{2}\right) + \left(LL - \frac{RA + LA}{2}\right) =$$

$$2RA - LA - LL + 2LA - RA - LL + 2LL - RA - LA = 0$$

A similar situation holds if Wilson's original technique is used. Here the three extremities are joined to form a central terminal. The sum of the extremity potentials so recorded is:

$$\left(RA - \frac{RA + LA + LL}{3}\right) + \left(LA - \frac{RA + LA + LL}{3}\right) + \left(LL - \frac{RA + LA + LL}{3}\right) =$$

$$3RA - RA - LA - LL + 3LA - RA - LA - LL + 3LL - RA - LA - LL = 0$$

Therefore, the characteristics of unipolar extremity leads, as recorded, cannot be used as a criterion of the accuracy of the Einthoven triangle hypothesis.

With respect to the method of proof advanced in this paper, the problem resolves itself into the question: "Is the fact that the mean potentials of the points of maximum (+) and (−) potential are equal to the mean potential of the extremities also due to construction, or is it actually a manifestation of the validity of the Einthoven hypothesis"? With respect to the answer to this, maximum (+) and (−) potentials can be obtained whether or not the body is a homogeneous conductor, whether or not the electrical activity of the heart is a dipole or some complex battery, whether or not the center of this electrical activity lies in the center of the body, and whether or not the extremities are equi-

EFFECT OF ATROPINE UPON THE PROLONGATION OF THE P-R INTERVAL FOUND IN ACUTE RHEUMATIC FEVER AND CERTAIN VAGOTONIC PERSONS

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IT HAS been suggested that a physiologic dose of atropine will shorten the P-R interval in heart block due to vagotonia and fail to do so in the heart block found in rheumatic fever. As a result of this conception, atropine has been used as a diagnostic test in cases of heart block, to differentiate between vagotonia and rheumatic fever. This practice has more or less persisted, even though Bruenn[1] showed, in 1937, that atropine shortened the prolonged P-R interval to normal in nineteen of twenty-two cases of acute rheumatic fever. In my experience with this procedure, it was soon observed that atropine did shorten the prolonged P-R interval in rheumatic fever, as observed by Bruenn, as well as in vagotonic persons. Inasmuch as many rheumatic fever cases and a fair number of vagotonic patients with prolonged P-R intervals were available, a comparative study was undertaken to ascertain definitely the value of atropine as a test to differentiate between the prolonged P-R interval of the vagotonic subject and the rheumatic fever patient.

PROCEDURE

Group 1.—Seventy-seven patients who had active rheumatic fever and whose electrocardiograms showed a P-R interval of 0.21 second, or longer, were studied. The patients were divided into two subgroups. Group 1A consisted of forty-three patients. They were given the following test: A control electrocardiogram was taken in the supine position, the patient was then given $\frac{1}{75}$ grain of atropine subcutaneously, and electrocardiograms were made at 20, 40, 60, and 120 minutes after the administration of atropine. It was found in this group (Group 1A) that the maximum shortening of the P-R interval occurred at the end of twenty minutes. In Group 1B, therefore, consisting of thirty-four patients, the same test was given with the exception that only a control tracing and one twenty minutes after the atropine were taken. The patients were kept flat in bed during the test period.

Group 2.—This group consisted of twelve vagotonic persons with prolonged P-R intervals. They were chosen to compare with Group 1, and were subjected to the same procedure as described previously.

RESULTS

Group 1.—Group 1A was observed over a two-hour period after $\frac{1}{75}$ grain of atropine. The P-R interval ranged from 0.21 to 0.32 second. Shortening of the P-R interval occurred in all of the forty-three cases and varied from 0.02 to 0.18 second (Fig. 1). The average shortening of the P-R interval for the entire group was 0.05 second. The maximum

Received for publication June 8, 1944.

mean potential of these two points equals zero if the Einthoven hypothesis is valid, extremity records obtained by using these two points as an indifferent electrode can be compared with the usual unipolar extremity lead records. Our observation that records so obtained and compared are identical allows us to conclude that the Einthoven hypothesis is valid, as is our method of obtaining unipolar leads.

APPENDIX

Lead II = Lead I + Lead III because of construction, and bears no relation to the validity of the Einthoven hypothesis.[6] It is due to the fact that, in Lead III, the connection of the left arm to the electrocardiograph is the reverse of its connection in Lead I. Therefore, Lead III records the difference of potential between the left arm and left leg, viz., LA − LL, whereas, in Lead I, the difference of potential between the right and left arms is recorded RA − LA. If these two leads are added together, the values of the LA cancel each other out, RA − LA + LA − LL = RA − LL, which is Lead II.

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were some rather unexpected effects upon the heart rate. The rate was increased in thirty-three, unchanged in two, and definitely slower in seventeen cases. There were frequent, transient variations in the amplitude and direction of the P waves after the atropine. There was a definite decrease in the amplitude of P_2 and P_3, and occasionally P_1, of short duration, in twenty-one of these cases. P_3 was inverted, temporarily, in seven instances. In one case, P_1, P_2, and P_3 became inverted

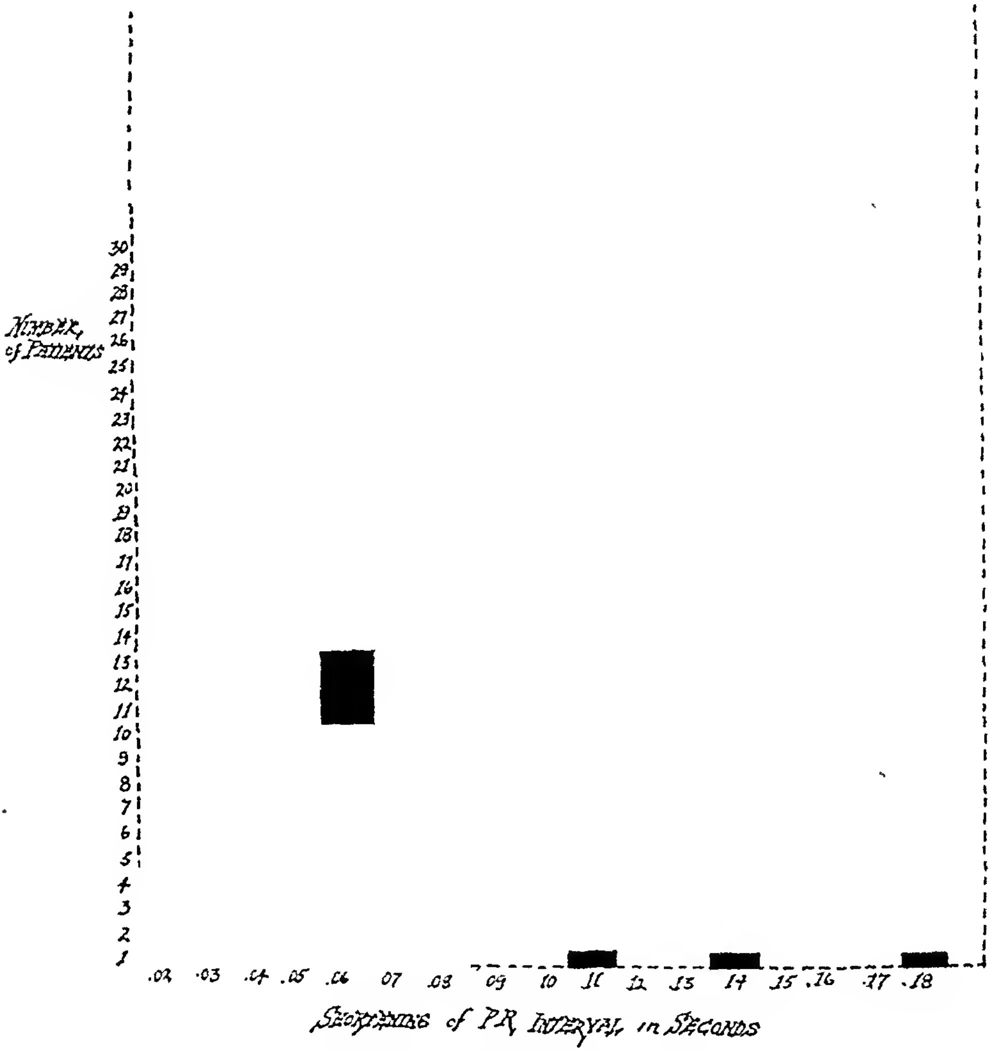
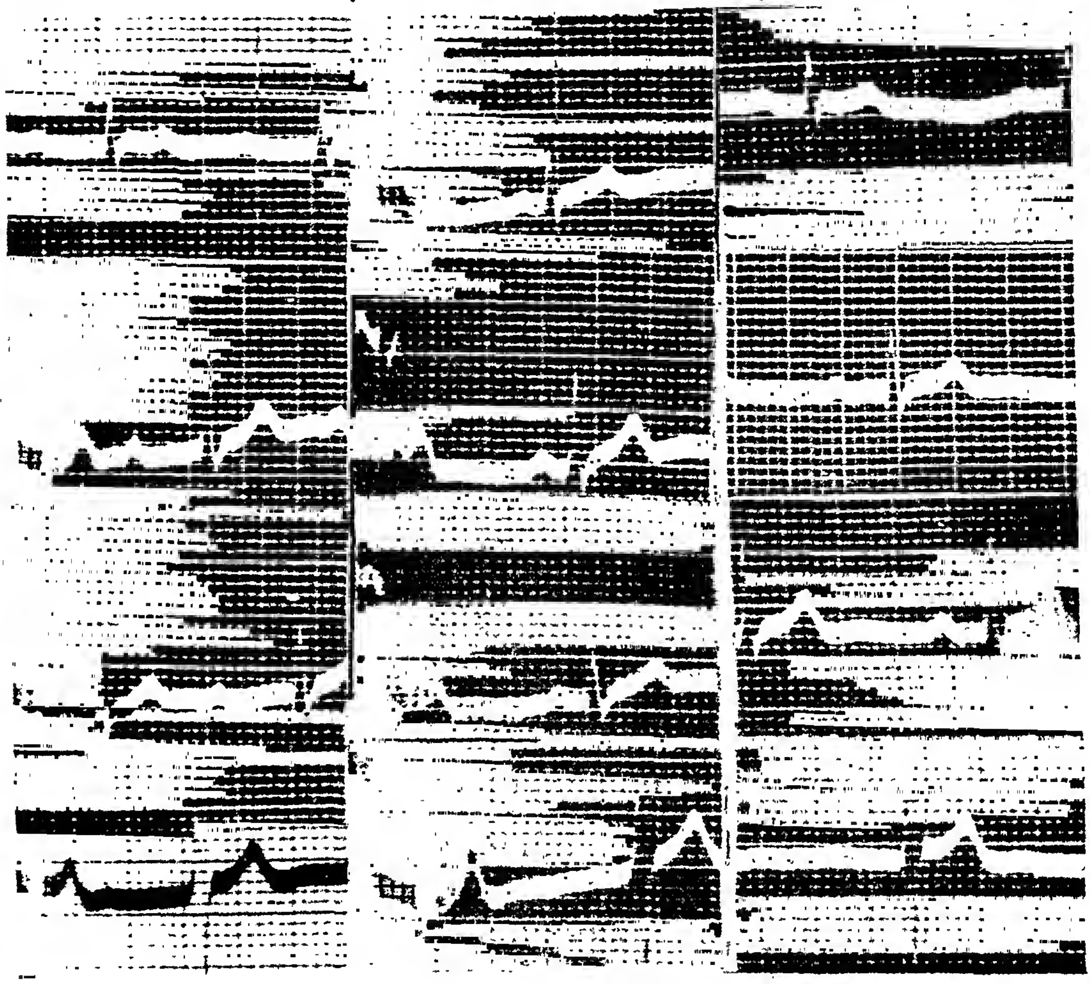


Fig. 2.—Chart showing the maximum shortening of the P-R interval in each of the seventy-seven cases in this study of rheumatic fever patients.

for a short time during the experiment (Fig. 3). There was no significant effect on the P waves in the remaining cases. Two patients with P-R intervals of 0.24 and 0.23 second, respectively, had temporary nodal rhythm twenty minutes after 1/75 grain of atropine subcutaneously.

In analyzing the cases used in this study, it became apparent that a majority of the patients were coming under observation after they had had rheumatic fever for more than two months. This was because patients in the acute stage of the disease were being retained in Station

shortening of the P-R interval occurred 20 minutes after giving the atropine in twenty-three cases, and 40 minutes after in twenty cases. The P-R interval returned to the control duration within 40 minutes after the atropine in one instance, within 60 minutes in seven cases, and within 120 minutes in seventeen cases. In the remaining cases, the P-R interval was still shorter than the control reading at the end of two hours.



a *b* *c*

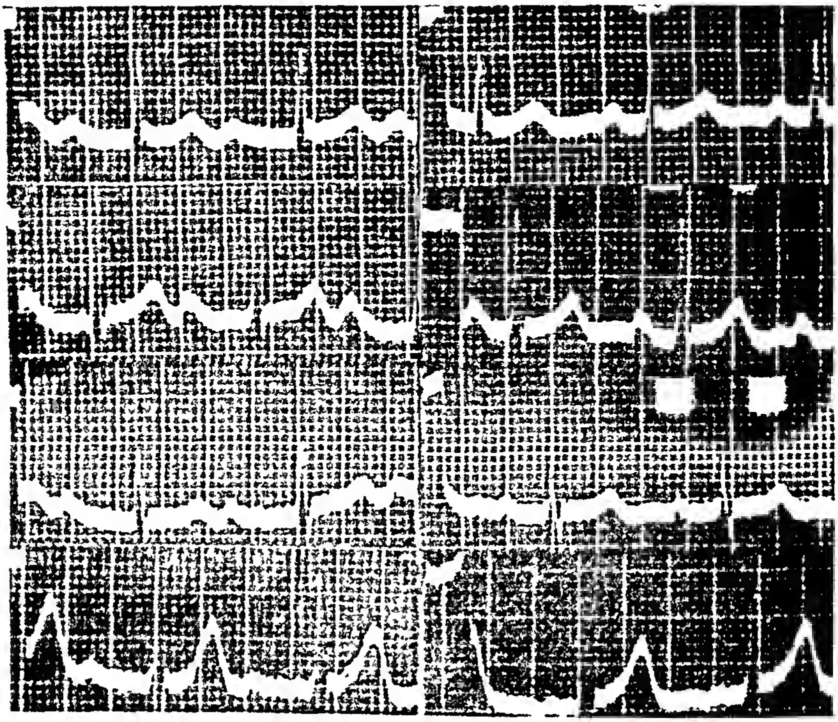
Fig. 1.—*a*, Shows a P-R interval of 0.30 second in a case of acute rheumatic fever. *b*, Tracing taken twenty minutes after 1/75 grain of atropine subcutaneously. The P-R interval has been shortened to 0.14 to 0.16 second. *c*, Two hours after the atropine the P-R interval is prolonged slightly to 0.20 to 0.22 second.

Group 1B was followed over a twenty-minute period after 1/75 grain of atropine. The P-R intervals ranged from 0.21 to 0.36 second. Shortening of the P-R interval occurred in each of the thirty-four cases in this group, and varied from 0.02 to 0.14 second, with an average of 0.047 second.

By combining Groups 1A and 1B, seventy-seven patients with rheumatic fever showed an average shortening of the P-R interval of 0.049 second after 1/75 grain of atropine hypodermically. Fig. 2 shows the maximum shortening of the P-R interval in each case in this group.

There was no significant effect on the QRS interval after giving atropine. In the cases which were followed over a two-hour period there

stages of rheumatic fever and in the following months of subacute activity, as long as the P-R interval is prolonged. It is in this latter group of cases that a test capable of differentiating between heart block produced by vagotonia and active rheumatic fever would be of definite benefit. In many cases the only sign of activity of rheumatic fever may be prolongation of the P-R interval months after the acute joint symptoms and fever have subsided. If the acute stages of the rheumatic fever were so mild as not to be recognized, it would be difficult to interpret prolongation of the P-R interval which was first detected several months after the onset of the disease.

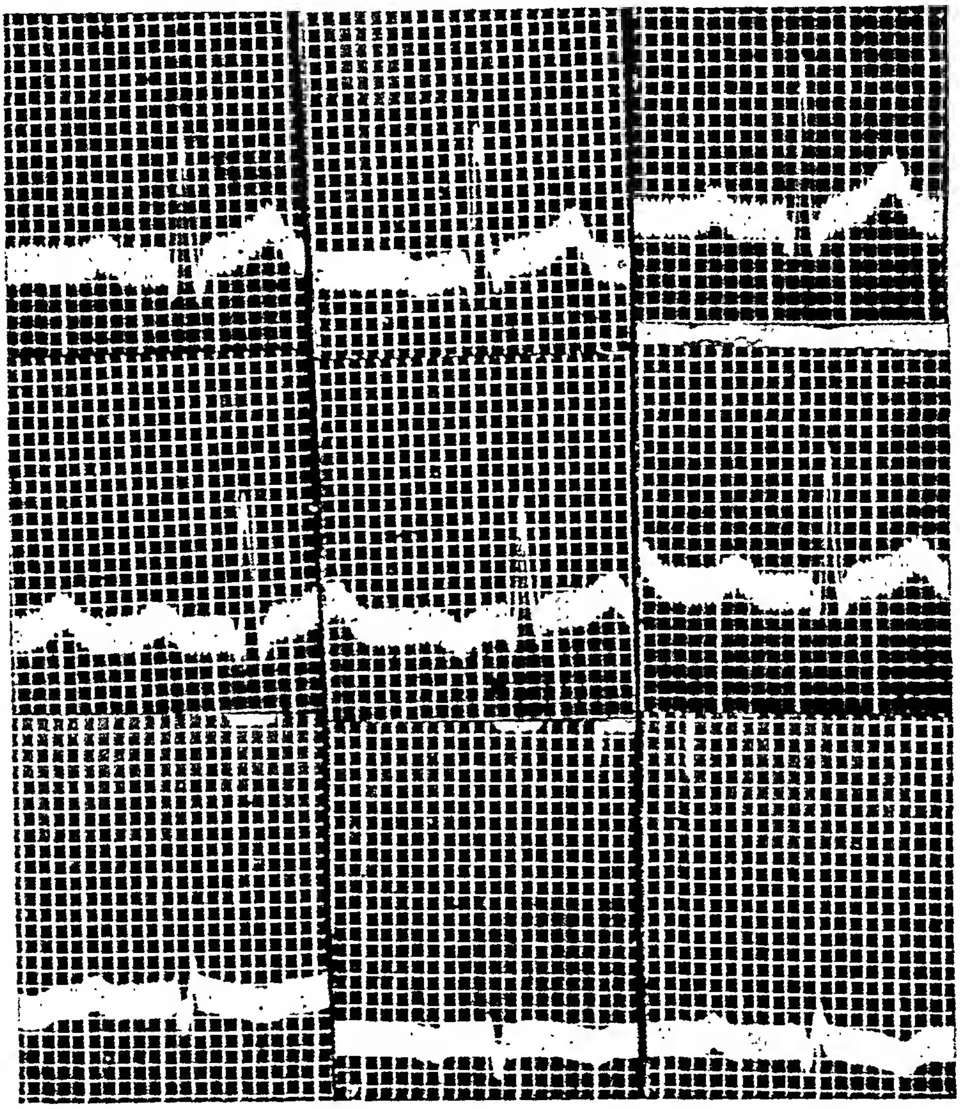


a b

Fig. 1.—*a*, This patient had neurocirculatory asthenia and marked vagotonia. P-R interval was 0.36 second before atropine. *b*, Twenty minutes after 1/75 grain of atropine subcutaneously the P-R interval was 0.20 second.

Group 2.—In order to ascertain whether there is any material difference in the reaction of rheumatic fever patients and vagotonic persons to atropine, a group of twelve vagotonic subjects with prolongation of the P-R interval was studied with the atropine test over a two-hour period. The age of these patients ranged from 18 to 34 years. Only one was over 26 years of age. There was no history of rheumatic fever, chorea, diphtheria, or the consumption of a drug in any case. There were no symptoms of degenerative heart disease. The blood pressure was normal in every instance. The heart was of normal size on physical examination and roentgenologically in each case. There were three that had soft, "functional," systolic murmurs in the pulmonic area. The temperature and sedimentation rates were normal. All presented the typical

Hospitals until it became evident that prolonged hospitalization would be necessary. For the purpose of ascertaining whether or not atropine shortened the P-R interval in the more acute stages of rheumatic fever, as well as in the subacute stage, the patients were classified according to whether they had been under observation during the first six weeks of their rheumatic fever or after two months. There were nineteen cases in which the atropine test was done during the first six weeks. The average shortening of the P-R interval in this group was 0.052 second.



a b c

Fig. 3.—*a*, Patient with acute rheumatic fever and a P-R interval of 0.24 second. *b*, The same patient, forty minutes after 1/75 grain of atropine subcutaneously, shows inverted P waves in Leads I, II, and III and a P-R interval of 0.18 to 0.19 second. *c*, Two hours after the atropine, the P waves are again upright and the P-R interval has returned to the control level of 0.24 to 0.26 second.

There were fifty-three cases in which the atropine test was done sometime between the second and ninth month of active rheumatic fever. The average duration of the disease in these cases was three and one-half months. The average shortening of the P-R interval in this group was 0.043 second. It is obvious from these studies of the two groups of cases that atropine shortens the P-R interval in both the very acute

THE EFFECT OF EXPERIMENTAL CORONARY ARTERY LIGATION ON THE COENZYME I AND COCARBOXYLASE CONTENT OF THE MYOCARDIUM OF THE DOG

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IT HAS been shown that breakdown of intracellular coenzymes occurs in shock and anoxia, and that this breakdown can be remedied by the administration of the corresponding vitamins.[1, 2] With this work as a background, we thought it would be interesting to investigate another important condition involving tissue anoxia, namely, that of coronary occlusion. When experiments on coronary ligation were begun, cocarboxylase was estimated in normal and ischemic cardiac muscle, as will be described, but no significant changes were demonstrable, contrary to the results obtained in previous studies of other tissues in shock.[1] When coenzymes other than cocarboxylase were considered, the fact that the heart is unable to metabolize lactate after coronary occlusion[3] suggested that coenzyme I, or diphosphopyridinenucleotide, the coenzyme of lactic dehydrogenase, might be destroyed. Since lactate is the preferential carbohydrate substrate for heart muscle,[4-6] a breakdown in its metabolism may be of importance from the standpoint of the viability of the ischemic cells. The fact that nicotinic acid deficiency produces electrocardiographic changes which are remediable by nicotinic acid administration[7] and are strikingly similar to electrocardiographic disturbances produced by coronary artery ligation[8] is further suggestive evidence that anoxia may produce coenzyme breakdown in heart muscle as well as in other tissues.

In order to ascertain whether or not such destruction of coenzymes does occur, both cocarboxylase and coenzyme I were estimated in normal and ischemic heart muscle, with and without the administration of nicotinamide, riboflavin, and succinate. The results of these experiments are presented here.

METHODS

Dogs which had been kept on a stock diet of Pard dog food for two weeks were anesthetized with pentobarbital sodium, administered intravenously. Under positive pressure artificial respiration the chest was opened via a midsternal incision, and the left anterior descending coronary artery exposed. In some cases the artery was dissected free and ligated, and in others a suture was passed beneath artery and vein, ligating both. (As will be seen, this apparently made no difference in

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This investigation was aided by a grant from the Dazian Foundation.
Received for publication June 10, 1944.

clinical picture of neurocirculatory asthenia with vagotonia. The P-R intervals ranged from 0.22 to 0.34 second. The atropine test on these patients resulted in a shortening of the P-R interval in each case, ranging from 0.04 to 0.16 second, with an average of 0.075 second (Fig. 4).

Although the average shortening of the P-R interval in these vagotonic cases was more marked than in those of rheumatic fever, the difference was not great enough to differentiate between the two conditions.

SUMMARY

1. Seventy-seven cases of active rheumatic fever with P-R intervals of 0.21 second, or longer, were studied. A control electrocardiogram was taken. The patients were then given $\frac{1}{75}$ grain of atropine subcutaneously, and subsequent tracings were taken at 20 minutes in thirty-four cases, and at 20, 40, 60, and 120 minutes in forty-three cases. There was shortening of the P-R interval in each instance, ranging from 0.02 to as much as 0.18 second. The average shortening of the P-R interval for the entire group was 0.049 second. These observations confirm those of Bruenn.[1] A temporary period of nodal rhythm was observed twenty minutes after the atropine in two cases. There was no significant effect on the interventricular conduction time. There was a transient effect upon the amplitude and direction of the P waves in twenty-nine cases, with a decrease in the amplitude of P_2 and P_3 in twenty-one cases, transient inversion of P_3 in seven cases, and temporary inversion of P_1, P_2, and P_3 in one case. The heart rate increased after atropine in thirty-three cases, diminished in seventeen, and remained unchanged in two cases.

2. Twelve vagotonic persons who had prolonged P-R intervals were also given the atropine test. There was shortening of the P-R interval in each case after atropine, ranging from 0.04 to 0.16 second, with an average of 0.075 second.

CONCLUSION

From these observations it seems clear that atropine cannot be used to differentiate between the prolongation of the P-R interval caused by vagotonia, on the one hand, and rheumatic fever, on the other, for the P-R interval is shortened by atropine in both of these conditions. These experiments present additional evidence that impairment of auriculoventricular conduction in acute rheumatic fever is due, in part at least, to an increase in vagal tone, as Bruenn[1] has suggested.

I wish to thank Colonel James S. Sweeney, M.C., Army of the United States, for his helpful interest and encouragement in carrying out this study.

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TABLE II

NICOTINAMIDE AFTER LIGATION

DOG	COENZYME I (γ/GRAM DRY MUSCLE)				COCARBOXYLASE (γ/GRAM DRY MUSCLE)		
	VESSELS LIGATED	NORMAL	ISCHEMIC	CHANGE (%)	NORMAL	ISCHEMIC	CHANGE (%)
14A	Artery	1,263	259	-79.5	42.3	41.4	- 2.1
14B	Artery	2,155	747	-65.4	52.4	48.9	- 6.7
16B	Artery	2,425	1,173	-51.7	26.3	30.9	+17.5
18A	Artery and vein	2,950	2,162	-26.7	31.8	47.4	+49.1
18B	Artery and vein	2,210	767	-65.3	45.0	47.3	+ 5.1
			Average	-57.7		Average	+12.6
		t = 2.16	p = > .05				

of the administration of 20 mg. of nicotinamide intravenously per kilogram of body weight one hour after the coronary artery had been ligated. It may be seen that there was apparently some decrease in coenzyme I breakdown when nicotinamide was administered after tying the vessel; the average breakdown was 57.7 per cent, but this decrease is not sufficiently marked to be statistically significant.

It occurred to us that perhaps the drug might not be reaching the ischemic area, for the heart muscle was rendered anoxic very suddenly, probably before significant collateral circulation could be established. Consequently, several dogs were given nicotinamide before the vessels were ligated. The results of these experiments may be seen in Table III.

After pretreatment with nicotinamide there was definitely less breakdown of coenzyme I; the average amount of breakdown was 31.8 per cent, as against 75.7 per cent in the controls. This difference is statistically significant ($p = < .01$).

Greig[2] has shown that, in shock, alloxazine adenine dinucleotide, the riboflavin containing coenzyme, is destroyed. This coenzyme is known to be necessary for the oxidation of reduced coenzyme I. Acting on the supposition that alloxazine adenine dinucleotide may also be destroyed in coronary occlusion, riboflavin* (5 mg. per kilogram of body weight) was administered with nicotinamide to four dogs before coronary

TABLE III

NICOTINAMIDE BEFORE LIGATION

DOG	COENZYME I (γ/GRAM DRY MUSCLE)				COCARBOXYLASE (γ/GRAM DRY MUSCLE)		
	VESSELS LIGATED	NORMAL	ISCHEMIC	CHANGE (%)	NORMAL	ISCHEMIC	CHANGE (%)
19B	Artery	1,820	1,570	-13.7	----	----	----
20A	Artery	2,850	644	-77.4	24.7	29.2	+18.2
20B	Artery and vein	1,930	1,412	-26.9	42.8	35.7	-16.6
21A	Artery	2,340	2,620	+12.0	32.3	33.0	+ 2.2
21B	Artery and vein	3,310	2,710	-18.2	32.5	28.8	-11.4
22A	Artery and vein	3,755	2,085	-44.5	32.5	40.7	+25.2
22B	Artery	3,725	1,830	-50.8	30.9	30.7	- 0.6
			Average	-31.8		Average	+ 2.8
		t = 3.68	p = < .01				

the coenzyme changes noted.) After this, the chest was closed by suturing.

In some experiments therapeutic agents were administered thirty minutes before the operation, in others, one hour after the ligation. In all cases, two hours after ligation of the vessel or vessels, the chest was reopened, the heart excised, and samples of myocardium removed from the ischemic area and from near-by normal areas of the left ventricular muscle.

These samples were quickly weighed, plunged into beakers of boiling water, and boiled for five minutes, after which the beakers were placed in a pan of ice water. After cooling, the samples were minced with scissors, homogenized, and the suspensions centrifuged. The supernatant fluid was analyzed for cocarboxylase* by the manometric method already described,[1] and for coenzyme I by the method of Axelrod and Elvehjem.[9] In some cases apozymase for the latter method was made by the method of Greig[2] from bottom yeast,† and in others apozymase was prepared from baker's yeast by our carbon tetrachloride method.[10]

The hearts of all dogs were examined after the muscle samples had been removed, in order to ascertain the amount of occlusion of the artery. Those animals in which the artery was found patent were discarded. Electrocardiograms taken on a few of the animals after the operation showed unmistakable evidence of coronary occlusion.

RESULTS AND DISCUSSION

Table I shows the results obtained in six experiments in which the left anterior descending coronary artery was ligated, with and without ligation of the accompanying vein. It will be seen that a consistent breakdown of coenzyme I occurred, varying in magnitude from 70 to 83 per cent of normal. No consistent change occurred in cocarboxylase, however. The importance in the metabolism of cardiac muscle of such a destruction of coenzyme I has already been pointed out.

TABLE I

CONTROLS

DOG	COENZYME I (γ/GRAM DRY MUSCLE)				COCARBOXYLASE (γ/GRAM DRY MUSCLE)		
	VESSELS LIGATED	NORMAL	ISCHEMIC	CHANGE (%)	NORMAL	ISCHEMIC	CHANGE (%)
7A	Artery	1,533	358	-76.6	77.4	44.8	-42.2
7B	Artery	1,737	394	-77.4	43.7	47.4	+ 7.8
8A	Artery and vein	2,090	603	-71.2	76.8	57.4	-25.3
8B	Artery and vein	2,595	442	-83.2	88.3	79.4	-10.1
9A	Artery	1,749	517	-70.6	52.5	47.0	-10.5
9B	Artery and vein	2,750	674	-75.5	64.3	73.0	+13.5
			Average	-75.7		Average	-11.1

Mann and Quastel[11] have shown that nicotinamide inhibits coenzyme I nucleotidase, the enzyme which breaks down coenzyme I in damaged brain tissue. It seemed logical to try this substance in order to reduce the amount of breakdown shown in Table I. Table II shows the result

*Cocarboxylase for use as reference standard in these estimations was kindly supplied by Merck and Company.

†Kindly supplied by Dr. Greig.

TABLE VI

SUCCINATE BEFORE LIGATION

DOG	COENZYME I (γ/GRAM DRY MUSCLE)				COCARBOXYLASE (γ/GRAM DRY MUSCLE)		
	VESSELS LIGATED	NORMAL	ISCHEMIC	CHANGE (%)	NORMAL	ISCHEMIC	CHANGE (%)
28A	Artery and vein	2,090	1,229	-41.2	29.5	33.4	+13.2
23A	Artery	2,365	697	-70.6	31.3	38.8	+24.0
23B	Artery and vein	2,345	1,187	-49.4	28.7	25.1	-12.6
27A	Artery and vein	1,700	1.695	- 0.3	33.3	40.2	+20.7
27B	Artery	3,510	2,285	-34.9	35.7	35.7	0
			Average	-39.3		Average	+ 9.1
		$t = 3.46$	$p = < .01$				

It will be noted that the control levels of cocarboxylase in these hearts were quite high, compared to those reported previously for other tissues. Also, one is surprised to see that no consistent change in cocarboxylase occurred under the experimental conditions reported here. That synthesis of cocarboxylase can go on in ischemic heart muscle, provided other coenzymes are reasonably intact, is suggested by Table IV, which shows that the ischemic sample in all four animals contained more cocarboxylase than did the control sample. Possibly the sluggish circulation in the ischemic muscle may have contributed to this by preventing the washing out of free nicotinamide, riboflavin, and thiamine.

Although we have presented evidence here that the administration of nicotinamide, riboflavin, and succinate can prevent the breakdown of coenzyme I which follows coronary ligation, it remains to be shown that these substances produce a beneficial effect on cardiac function after such a procedure. This problem, together with analyses of other possible metabolic failures in experimental coronary occlusion, is being investigated.

SUMMARY

1. Coenzyme I is destroyed to the extent of 70 to 83 per cent of normal in cardiac muscle rendered ischemic by coronary artery ligation.

2. Nicotinamide, nicotinamide and riboflavin, and succinate, when administered intravenously before coronary ligation, protect to a great extent against such breakdown of coenzyme I.

3. Nicotinamide and succinate are only fairly efficient in remedying this destruction when injected after the occlusion has been established.

4. No significant change in tissue cocarboxylase occurs after coronary ligation.

The author wishes to express his gratitude to Dr. Herbert S. Wells and Dr. Tinsley R. Harrison for their very helpful criticism and suggestions.

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TABLE IV

RIBOFLAVIN AND NICOTINAMIDE BEFORE LIGATION

DOG	VESSELS LIGATED	COENZYME I (γ/GRAM DRY MUSCLE)			COCARBOXYLASE (γ/GRAM DRY MUSCLE)		
		NORMAL	ISCHEMIC	CHANGE (%)	NORMAL	ISCHEMIC	CHANGE (%)
24A	Artery and vein	4,090	3,300	−19.3	32.0	37.3	+16.6
25A	Artery and vein	1,862	1,105	−40.6	27.5	35.6	+29.4
25B	Artery	1,690	1,050	−37.8	31.0	34.2	+10.3
26A	Artery and vein	2,190	1,424	−35.0	37.7	41.3	+ 9.5
			Average	−33.2		Average	+16.5
		$t = 9.57$	$p = < .01$				

ligation. Although these experiments showed 33.2 per cent breakdown of coenzyme I, which was slightly more than the amount after pretreatment with nicotinamide, there was much less variation among the dogs receiving both vitamins, and the difference was statistically much more significant (p = much less than .01).

Succinic acid is a C_4 dicarboxylic acid which can be metabolized directly by the cytochrome-cytochrome oxidase system without the help of the coenzymes discussed previously. Thus, the administration of this substrate might be supposed to supply sufficient energy to keep the cell intact, and perhaps to allow resynthesis of some of the coenzymes broken down in anoxia. Proger[12] has demonstrated an increase in oxygen uptake by homogenized heart muscle in the presence of succinate, even in an atmosphere of reduced oxygen tension. He also points out that succinate is often able to prevent anoxic electrocardiographic changes in dogs.

We have administered sodium succinate (1 Gm. per kilogram of body weight) intravenously to dogs, before and after coronary ligation. As may be seen in Tables V and VI, there was a significant reduction in coenzyme I breakdown ($p = < .01$) when the substance was given before ligation; the average breakdown was 39.3 per cent. When injected after coronary occlusion, the amount of breakdown averaged 48.7 per cent, which is statistically only moderately significant ($p = < .05$).

TABLE V

SUCCINATE AFTER LIGATION

DOG	VESSELS LIGATED	COENZYME I (γ/GRAM DRY MUSCLE)			COCARBOXYLASE (γ/GRAM DRY MUSCLE)		
		NORMAL	ISCHEMIC	CHANGE (%)	NORMAL	ISCHEMIC	CHANGE (%)
11A	Artery and vein	2,860	2,705	− 5.3	53.8	57.1	+ 6.1
12A	Artery	2,400	1,319	−45.4	44.9	45.6	+ 1.6
12B	Artery	2,340	725	−68.2	44.8	52.0	+13.9
13A	Artery	2,860	1,039	−63.7	37.7	34.3	− 9.0
13B	Artery and vein	1,940	414	−78.6	33.7	30.1	−10.7
15	Artery	3,050	2,100	−31.1	28.7	28.6	− 0.3
			Average	−48.7		Average	+ 0.3
		$t = 2.40$	$p = < .05$				

THE EFFECT OF DIATHERMY ON CORONARY FLOW

An Experimental Study on Dogs

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During the past thirty years numerous articles have reported the beneficial results of diathermy in the treatment of angina pectoris. In 1911, Nagelschmidt[1] reported a small series of patients with angina pectoris who apparently were definitely improved after a series of treatments with high frequency current. Nagelschmidt concluded this report by saying, "It is most remarkable to see how patients in a very grave condition recover immediately under the influence of diathermy. In a few seconds or minutes all trouble ceases, no oppression, no pain, no restlessness, no feeling of anguish." Again, in 1928, Nagelschmidt[2] indicated his enthusiasm when he stated, "I do not know of any other medicament or any other method which would be able to cut off so severe an attack in so very few moments of application as with diathermy." Stewart,[3] in 1926, reported, "There is no question that diathermy through the heart will improve the coronary circulation and minimize the effect of toxin on its muscular structure." Laubry, Walser, and Meyer,[4] in 1937, reported their results with diathermy in the treatment of angina pectoris. Of the fifty-six patients so treated, 40 per cent obtained very good results, and 20 per cent, fair results. They pointed out that short waves were much superior to long waves, and that best results were obtained in angina of effort. Wolf,[5] in his textbook of physical therapy, states, "If we take into consideration the physiological action of diathermy, that it raises the temperature of the tissue and thus dilates vessels, we can a priori state that it will be helpful in all those cases of angina pectoris which are due to a narrowing of the coronary vessels, be it by sclerotic process or by spasms." Siegen[6] treated 770 patients with angina pectoris, employing short wave diathermy in addition to other routine forms of therapy, and reported his results in 1937. Forty-three per cent of the 770 patients were reported as cured, 54 per cent were improved, and only 3 per cent were uninfluenced. In addition to the subjective improvement noted by the patients, he presented serial electrocardiograms which showed "evident improvements." Similarly, Hyman[7] treated 87 patients with symptoms of coronary thrombosis and noted "improvement" in the electrocardiogram, as well as improvement clinically after a series of diathermic treatments. Blackman and Richardson[8] stated that short wave

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Received for publication June 16, 1944.
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cylinder, the volume of the blood flow was readily calculated. Heparin was used to prevent coagulation. The blood was returned by way of the femoral vein and kept at a constant rate of flow, temperature, and pressure. The blood pressure was recorded from the carotid artery by a mercury manometer. (Typical curves obtained are shown in Figs. 1 and 2, taken from Dog 4, Table I.)

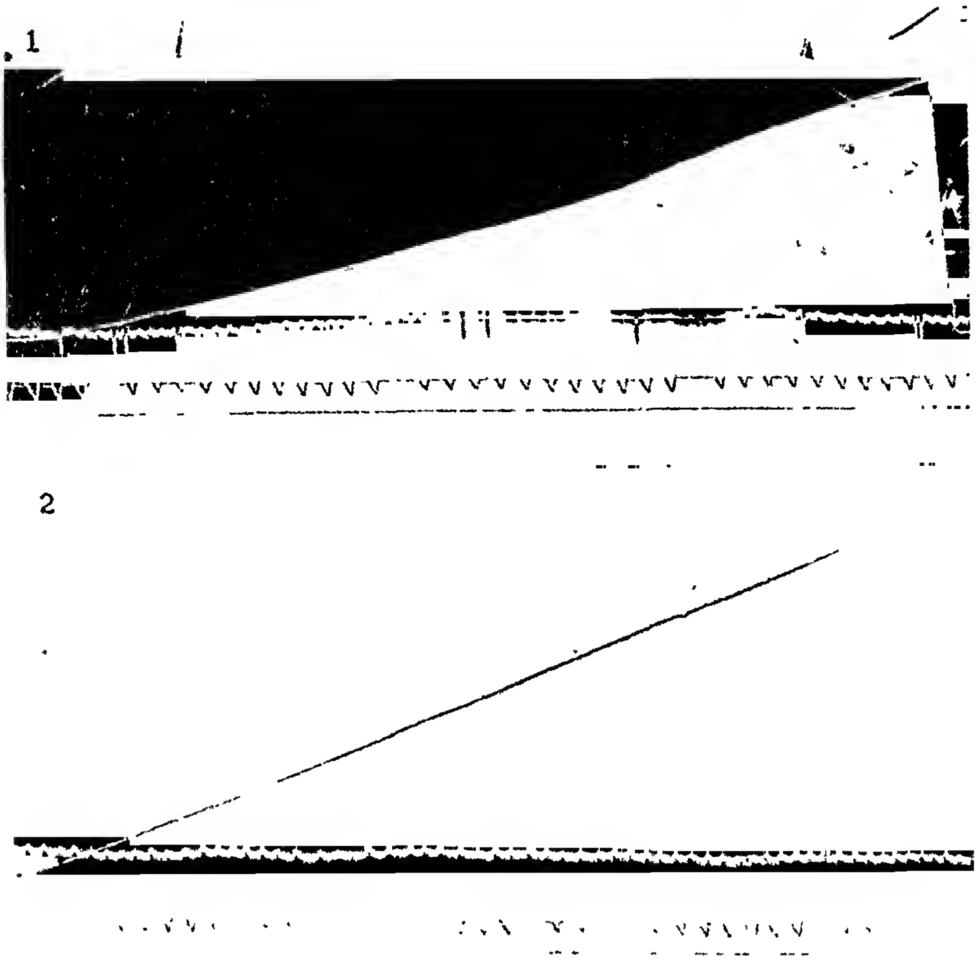

Fig. 1.—The slowly rising gradient represents the rise of blood in the cylinder of the piston recorder. When the cylinder becomes full it is emptied manually, and thus the rapid fall. The vibratory line represents the blood pressure recording. The automatic timer was set at five seconds. Graph *1* represents coronary flow at the start of the experiment. In the middle portion of this tracing there is a rather sharp rise in the gradient. At this point theobromine was injected intravenously, and the rise indicates that there is an increase in the coronary flow and that the cannula is in the coronary sinus and is functioning properly. Graph *2* is the control curve, taken two minutes after theobromine injection and just prior to application of the inductotherm.

After the coronary flow had become stabilized, an 8-inch inductotherm disk[16] was placed on the precordial area. Several thicknesses of burlap were placed between the chest wall and the disk to act as a dielectric. The machine was arbitrarily set at 100[16] and applied for one-half hour. Eleven animals were used for the experiment, four of which were controls. In two of the controls no heat was applied, in the third a hundred-

diathermy is the most efficient and reliable agent available for improving the blood supply to the myocardium in cases of coronary thrombosis, and they felt that clinical evidence shows that diathermy allays spasm, induces coronary dilatation, and develops new blood pathways. Ferrario[9] states, "In general, patients with the syndrome of angina pectoris improve notably under short wave treatment." Hay and Ince,[10] Joslyn,[11] Brow,[12] Cignolini,[13] and many others have reported favorably on this type of treatment. Bearman,[14] on the other hand, points out that it is difficult to prove that there is any special value in the use of the short wave current in the treatment of angina pectoris because spontaneous remissions occur in the disease and because rest and other measures are applied concurrently.

It is evident that the majority of reports are enthusiastic about the beneficial effects of diathermy on symptoms attributed to coronary insufficiency. These reports, however, are confined for the most part to clinical observations or electrocardiographic interpretation.

The purpose of this study was an attempt to ascertain experimentally the effect of diathermy on coronary flow in the dog.

As a preliminary experiment, the temperature of the heart muscle of the dog after applying diathermy over the heart was measured. A thermocouple was inserted into the musculature of the right ventricle through the opened chest wall. The chest was then tightly closed. The control temperature was 96.2° F. for a period of ten minutes. Diathermy was then applied over the precordial region for one-half hour. Immediately after this application, the temperature rose to 104° F. This elevation in temperature was accounted for by the heating of the thermocouple in the high frequency induction field. One-half minute temperature readings were recorded to secure a cooling curve during the next three minutes, and at the end of this time the temperature had fallen to what was probably a true level, namely, 102.3° F. This result indicated that the temperature of the heart was elevated by the application of diathermy through the chest wall.

The coronary flow was measured on the intact animal, using the technique described by Gilbert and Fenn.[15] Despite past criticism of this method, we felt that it was most applicable to the problem under consideration.

Dogs weighing 13 to 14 kilograms were used. One-half hour before operation the animals were given 0.25 c.c. of a 4 per cent solution of morphine sulfate per kilogram of body weight. Grehant's mixture (5 per cent chloroform in 50 per cent alcohol) was given a few minutes before operation by means of a stomach tube. The anterior chest wall was opened at the right costochondral junction. The parietal pleura was opened, and oxygen was administered by means of a tracheal cannula under positive pressure to prevent atelectasis. The coronary sinus was then cannulated with a modified Morovitz cannula which was connected to the cylinder of a piston recorder. With a known volume of the

TABLE I

DIATHERMY OVER PRECORDIAL AREA FOR ONE-HALF HOUR

DOG	CORONARY FLOW (C.C./MIN.)	BLOOD PRESSURE (MM. HG)	HEART RATE PER MINUTE	CHANGE IN CORONARY FLOW (C.C./MIN.)
		Control readings		
1	25.2	34/30	159	
2	7.2	42/35	96	
3	13.2	35/29	150	
4	19.8	28/25	114	
5	17.4	26/24	108	
6	18.0	19/16	130	
7	14.5	27/23	93	
		Readings at the end of experiment		
1	28.8	22/20	220	3.6+
2	21.6	19/16	132	14.4+
3	18.0	30/21	135	4.8+
4	28.8	32/28	144	9.0+
5	22.2	29/22	120	4.8+
6	20.4	19/17	135	2.4+
7	12.6	26/22	111	1.9-

TABLE II

CONTROL ANIMALS

DOG	CORONARY FLOW (C.C./MIN.)	BLOOD PRESSURE (MM. HG)	HEART RATE PER MINUTE	CHANGE IN CORONARY FLOW (C.C./MIN.)
		Control readings		
1	13.5	48/45	117	
2	10.8	34/21	75	
3	20.7	49/44	145	
4	18.0	31/26	142	
		Readings at end of experiment		
1	22.2	29/26	105	8.7+
2	18.0	27/24	66	7.2+
3	23.4	44/42	155	2.7+
4	21.6	28/23	142	3.6+

Dog 1. Diathermy over lower part of abdomen for thirty minutes.
Dog 2. 100-watt electric light bulb over precordial area for thirty minutes.
Dogs 3 and 4. No heat applied. Final readings taken one-half hour after control readings.

which could have produced an increase in coronary flow. In Dogs 3 and 6, Table I, and Dogs 1, 2, and 4, Table II, the increase in the coronary flow could not be explained by either changes in the blood pressure or the heart rate. This increase in flow was apparently due to the development of acidosis, as suggested by Gilbert and Fenn.[15, 17]

CONCLUSION

1. The effect of applying diathermy over the heart on the coronary flow of the dog was measured.

2. As measured by this method, no significant increase in the coronary flow was demonstrated.

watt electric light bulb was used as a source of heat and placed over the precordial area for one-half hour, and, in the fourth, the inductotherm disk was placed over the lower part of the abdomen.

The results are summarized in Tables I and II. It will be noted that, of the animals which received diathermy over the precordial area (Table I), there was an increase in the coronary flow in all except one, in which there was a slight decrease. It would thus appear that the short wave

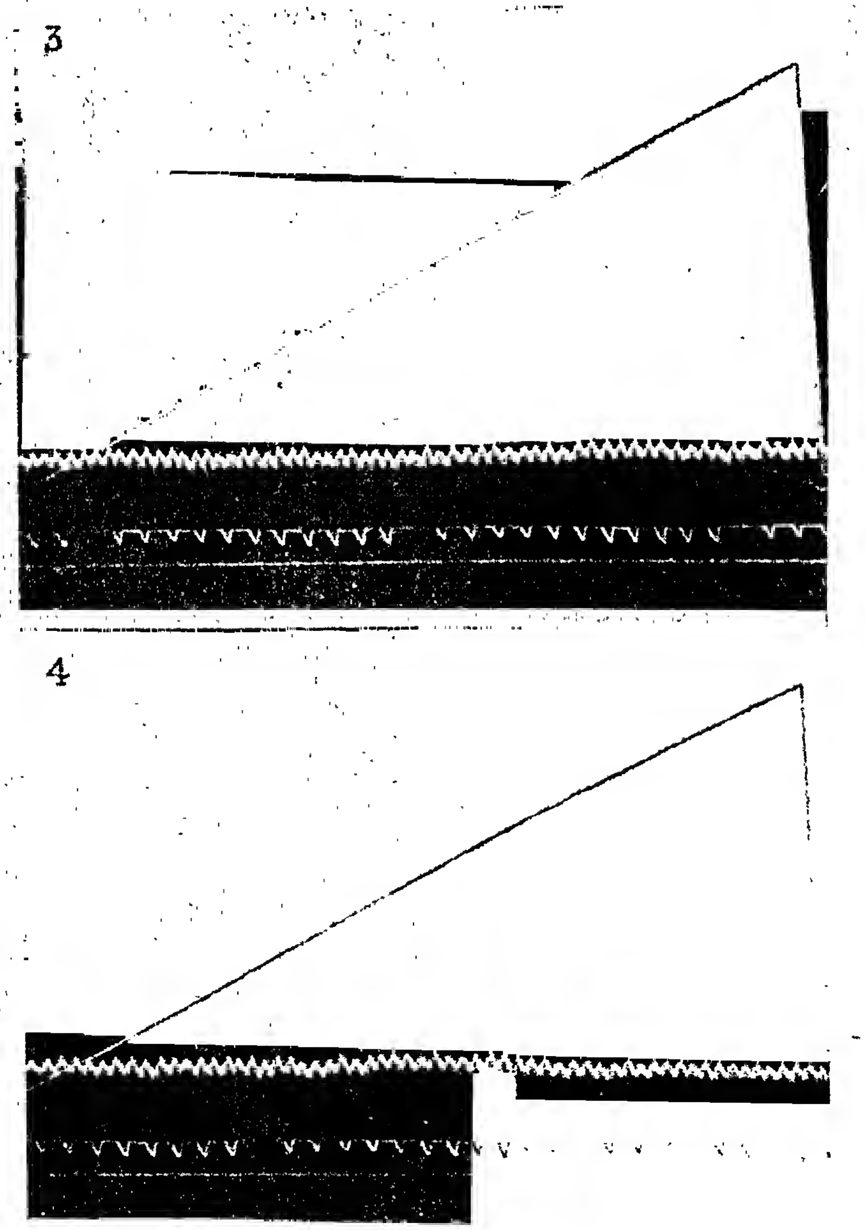

Fig. 2.—Graphs 3 and 4 represent coronary flow after one-half hour of application of the inductotherm over the precordial area. It is evident that coronary flow has increased over the control.

current increased coronary flow. However, in the controls there was also an increase in the coronary flow which was as marked as when diathermy was applied to the heart itself.

In some instances this increase could be explained by an increase in heart rate as noted in Dogs 1, 2, 4, 5, and 7, in Table I, and Dog 3 in Table II. In Dogs 4 and 5, Table I, there was a rise in blood pressure

SUGAR TOLERANCE IN NEUROCIRCULATORY ASTHENIA

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IN MAY, 1943, when we were seeing a large number of soldiers with neurocirculatory asthenia, we first became impressed with the marked similarity between the symptoms of neurocirculatory asthenia and those of hypoglycemia. This report covers a study of the glucose tolerance curves which was carried out over the ensuing seven months at Torney General Hospital. There is one striking difference in the histories of patients with neurocirculatory asthenia and those with true hypoglycemia, namely, the regular occurrence of the latter several hours after meals, and prompt relief with the ingestion of carbohydrates, and the absence of such a history in neurocirculatory asthenia. Dorst[1] carried out a similar study in 1936. He found that the person with neurocirculatory asthenia had a flat tolerance curve, whereas the sthenic type had a normal curve. He further demonstrated that the former type of person gained weight, and rapidly developed a normal tolerance curve on insulin therapy. His further work demonstrated a similar, flat curve in neurasthenic persons in general. He believes the flat curve is common enough to be of diagnostic value in the "Effort Syndrome," and suggests that the continued low blood sugar level may account for the characteristic asthenia in this group.

The report herewith rendered is in large part confirmatory of Dorst's results, although we do not agree that the low sugar values are responsible for the asthenia. This disagreement is based on three facts: Not all the patients who suffer from typical neurocirculatory asthenia have low values; none of the symptoms, including asthenia, is improved at any time by the administration of sugar; one patient in our group with typical neurocirculatory asthenia had diabetes mellitus with high blood sugar values.

This report covers the study of forty patients. Each patient was thoroughly examined from a clinical and laboratory standpoint, including chest roentgenogram, electrocardiogram, blood cholesterol, basal metabolic rate, heart rate while asleep, urine concentration and urea clearance, blood cell count, urine, Kahn reaction, and numerous blood pressure readings. Heart disease and hyperthyroidism were adequately excluded in all cases. Every patient had symptoms and signs typical of neurocirculatory asthenia, consisting of shortness of breath, sharp precordial pain, palpitation, "blackouts," asthenia, headache, poor appetite, tachycardia when awake, tremor, marked dermographism, and hyperhidrosis, particularly of the hands, feet, and axillae.

Six-hour glucose tolerance tests were done on all patients; a fasting specimen was followed by hourly specimens for six consecutive hours after the oral administration of 100 Gm. of glucose, except in seven of

Received for publication June 18, 1944.

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Clinical Reports

PAROXYSMAL AURICULAR TACHYCARDIA DUE TO RECIPROCAL RHYTHM

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THE mechanism of re-entry is believed to explain an extrasystole which is firmly bound to a preceding beat, coming always after a fixed interval. De Boer[1] invoked re-entry as an explanation of extrasystoles, and Lewis[2] agrees that single extrasystoles may be due, on occasion, to re-entry. Lewis also states that re-entry is possible in the auricle, A-V node and the ventricle, accounting for auricular, nodal, and ventricular extrasystoles. Another form of re-entry is reciprocal rhythm, i.e., an impulse is conducted from the A-V node or ventricles to the auricles, finds an auricular by-pass, and is transmitted again to the ventricles. Katz[3] asserts that reciprocal rhythm should be diagnosed only when two ventricular complexes within 0.5 second of each other have a bizarre P interposed between them. A mechanism of this nature, he asserts, can conceivably continue for some time and give rise to a tachycardia which is similar in all respects to supraventricular tachycardia. We have recently studied a case which illustrates the above mechanisms and presents certain other peculiar features.

REPORT OF CASE

The patient was a 40-year-old schoolteacher who suffered from gradually progressing paraplegia of one year's duration caused by a spinal tumor which was removed at operation. For the preceding five years he had complained of very frequent spontaneous attacks of rapid palpitation, lasting for variable periods of time, ranging from minutes to a few hours, although not of a disabling nature. Clinically, simple paroxysmal tachycardia was diagnosed; it could be readily arrested by carotid sinus pressure. Digitalis in saturating doses kept the tachycardia well under control; on the other hand, quinidine (taken in 0.2 Gm. doses five times daily for a period of three days) definitely aggravated and perpetuated the tachycardia, and interfered with the otherwise prompt response to carotid sinus pressure. Electrocardiograms were taken during the tachycardia, and the effect of pressure on the right carotid sinus was demonstrated; another series was taken in the intervals of spontaneous freedom from the attacks.

Analysis of the records revealed the following peculiar arrhythmia.

Received for publication Nov. 17, 1943.

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the cases, in which five specimens were examined at hourly intervals. One of these seven had a diabetic curve. The other six were the earliest ones done, and since the curve was still falling at the end of four hours, we decided to prolong the test on later ones. In all but seven of these thirty-two cases, the level at six hours was greater than at five hours. In five of these the reading was the same as at five hours; in one it was 2 mg., and, in the other, 7 mg., lower. The Folin Wu technique was used for the carbohydrate estimations.

Curves were classed as low if the highest single reading was under 140 mg. per cent. Of the forty patients, twenty-six, or 65 per cent, were classified as having low curves. The highest level attained in these twenty-six cases is shown in Table I.

TABLE I

BLOOD SUGAR LEVEL MG. PER CENT	NUMBER OF CASES
131-140	1
121-130	7
111-120	5
101-110	5
91-100	5
81-90	3

In most of the curves with peaks of 120 or more, there was only one such reading, and the rest of the curve was below 100. Eleven had normal curves, two were questionably diabetic, and one was definitely diabetic.

Several of the patients were given candy when they felt weak or faint, but in no instance did this procedure improve the faintness, even temporarily. Furthermore, there was no relationship between eating and the appearance of "blackout" spells. Sometimes these spells would come on immediately, or shortly, after a meal rich in carbohydrate.

COMMENT

This study is confirmatory of Dorst's work. A flat tolerance curve is present in a sufficiently high percentage of cases to be of value in the diagnosis of neurocirculatory asthenia. The explanation of this is not immediately apparent, but, in our opinion, the low sugar levels do not cause the symptoms in this psychoneurotic syndrome. Dorst has further shown that a similar curve is present in other psychoneuroses.

CONCLUSIONS

Sixty-five per cent of forty patients with typical symptoms of neurocirculatory asthenia showed flat sugar tolerance curves. It has been found that the test is of some value in confirming the diagnosis, but, in our opinion, the low sugar levels are not responsible for the symptoms.

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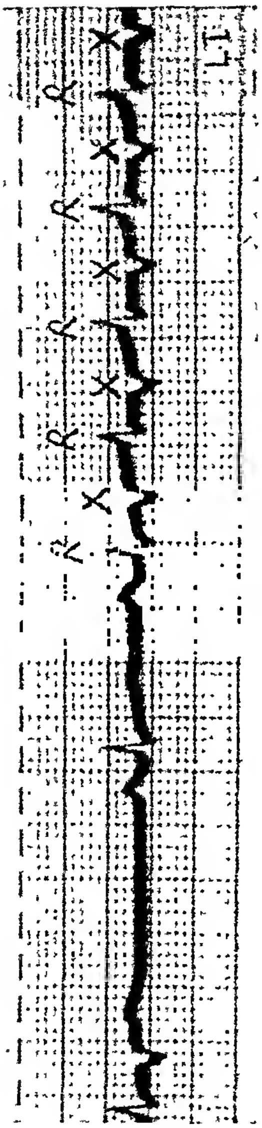

Fig. 3.

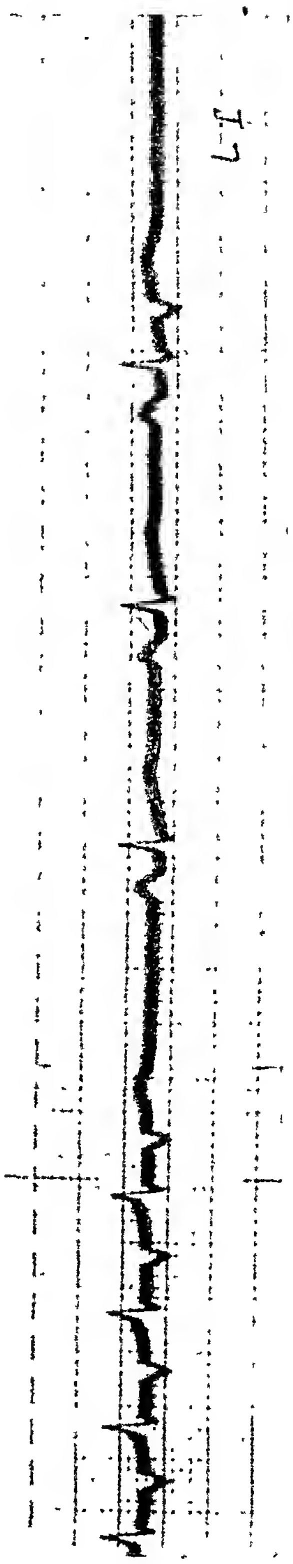

Fig. 4.

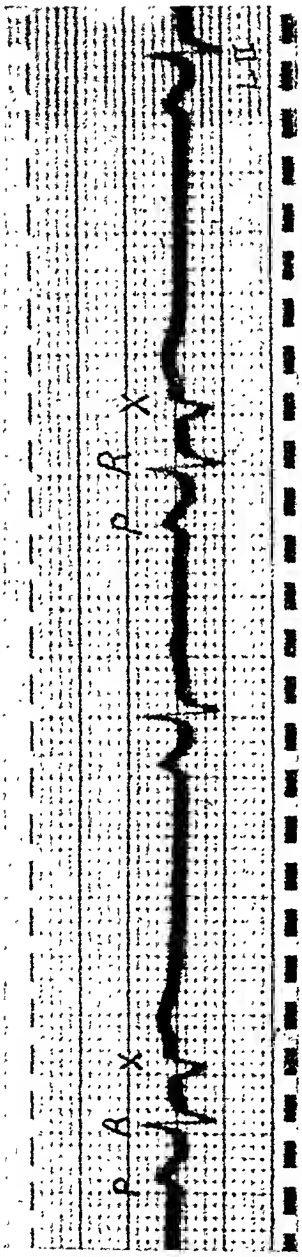

Fig. 1.—The fine vertical lines are 0.04 second apart. The distance between horizontal lines, at the standardization used, represents 0.1 millivolt. The same values apply to the other figures.

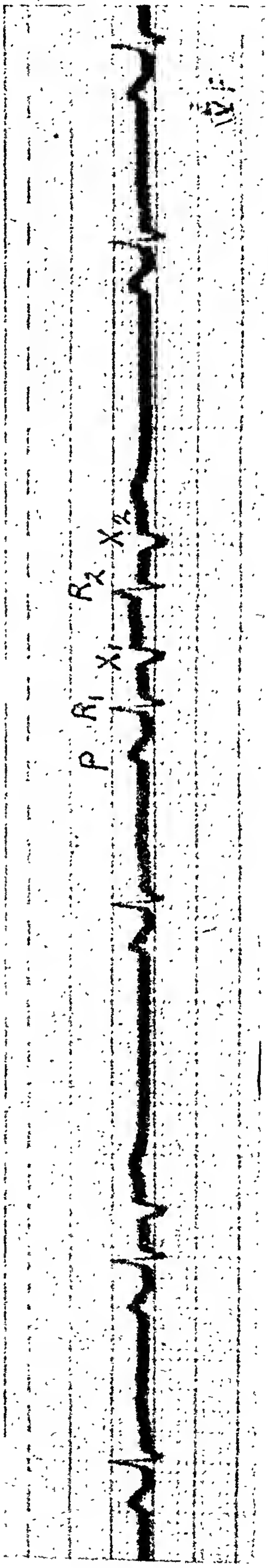

Fig. 2.

fractory period of the junctional tissues (spontaneous or induced by carotid sinus pressure) led to blocking of these auricular extrasystoles, which inevitably ended the attack.

4. Actually, when an attack ended in this case, it did so with a blocked auricular extrasystole. It is argued that, if the paroxysmal tachycardia be due to the sporadic activity of an ectopic pacemaker, cessation of the attack would occur when that ectopic pacemaker stopped its sporadic discharge. Blocking of the auricular beats would have no effect on their genesis from the ectopic pacemaker.

5. It is also interesting that digitalis, presumably by interfering with conduction of the stimulus between the auricles and ventricles, controlled the attacks well. Quinidine, on the other hand, failed in this respect quite markedly. This is not easy to explain, but it may have been due to its vagal effect, paralysis of which improves conduction, and so perpetuates the attacks.

SUMMARY

A case of arrhythmia is analyzed and discussed in detail, and evidence is offered to indicate that the following were factors in producing the arrhythmia:

1. *Blocked Auricular Extrasystoles.*—Re-entry into the auricle from a ventricular by-pass; the re-entrant waves were not transmitted back again to the ventricles.

2. *Conducted Auricular Extrasystoles.*—Re-entry into the auricles from a ventricular by-pass; the re-entrant waves were transmitted back into the ventricles, i.e., reciprocal rhythm.

3. *Attacks of Auricular Paroxysmal Tachycardia.*—A continuously circulating wave of excitation between the ventricles and auricles, i.e., reciprocal rhythm perpetuated over some length of time.

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Fig. 1 shows Lead II, which was taken during one of the intervals between the paroxysms of tachycardia. It reveals normal sinus rhythm, disturbed every now and then by an auricular extrasystole which is blocked because of its prematurity.

Measurement of the P-X interval (the time from the beginning of P to the beginning of the following extrasystole) and the R-X interval (the time from the beginning of QRS to the beginning of the following extrasystole) showed that the former was 0.47 second, and the latter, 0.25 second.

Fig. 2 (Lead IVF) shows an auricular extrasystole which was conducted to the ventricle. This conduction may be accounted for by slight changes in the refractory period of the junctional tissues, enabling the impulse to pass to the ventricle and elicit a response. P is followed by R_1, and this is followed by X_1 (an auricular extrasystole), which is conducted to the ventricle (R_2); this is followed by X_2, which is blocked.

The time relations in this series are as follows: $P\text{-}X_1 = 0.46$ second, $R_1\text{-}X_1 = 0.24$ second, $X_1\text{-}X_2 = 0.52$ second, $R_2X_2 = 0.24$ second.

Fig. 3 shows Lead I during an attack of paroxysmal tachycardia, during which the X-X interval is 0.42 second, and the R-X interval, 0.24 second.

Fig. 4 (Lead I) shows spontaneous cessation of one of the attacks of tachycardia, with a blocked auricular beat. The time intervals are exactly the same as in Fig. 3.

DISCUSSION AND COMMENT

1. Consideration of the time relations shown previously will make it quite evident that there was a fixed coupling of auricular extrasystoles to preceding ventricular beats. The R-X intervals were strikingly constant (0.24 to 0.25 second), whereas the P-X and X-X intervals varied from 0.46 second to as much as 0.52 second. This fixed time relation of auricular extrasystoles to preceding ventricular beats, which implies a causal relationship, makes it difficult to avoid the conclusion that a re-entrant wave of stimulus formation from the ventricle into the auricle was responsible for the fixed coupling.

2. Further evidence of this is the interesting fact that an auricular extrasystole never followed another blocked auricular extrasystole. It would appear that an auricular extrasystole could not occur unless the impulse of the auricular beat, whether from the sinus or premature stimulus, entered the ventricle. Only when this occurred was the by-pass reached along which re-entry to the auricle could take place.

3. During paroxysms of tachycardia (Fig. 3) the X-X intervals were 0.42 second, whereas the R-X intervals were still 0.24 second, showing again the close coupling of auricular to preceding ventricular beats. The paroxysms of auricular tachycardia thus appeared to be due to re-entry through the ventricular by-pass into the auricle, leading to an auricular extrasystole, which re-entered again through an auricular by-pass, and was conducted to the ventricles; the cycle was repeated in this order for a variable period of time, until some increase in the re-

days, when he developed signs of renal irritation and this drug had to be discontinued. His blood level of sulfadiazine on the last day of this therapy was 13.6 milligrams. Two subsequent blood cultures were taken, both of which failed to reveal any growth of *Staph. aureus*. He was discharged from the hospital Nov. 23, 1943. The diagnosis at this time was rheumatic heart disease, with aortic and mitral insufficiency, and *Staph. aureus* bacteremia, probably with bacterial endocarditis. The patient was transferred to New York City and admitted to the Post-Graduate Hospital on Dec. 3, 1943. The subsequent hospital record is summarized in the graphic charts.

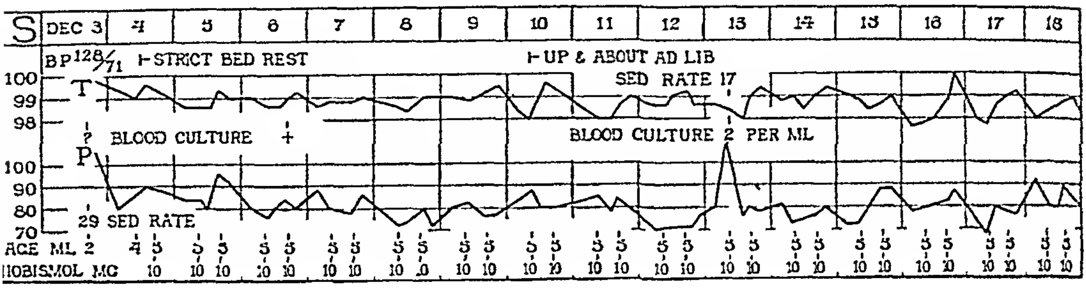

Fig. 1.

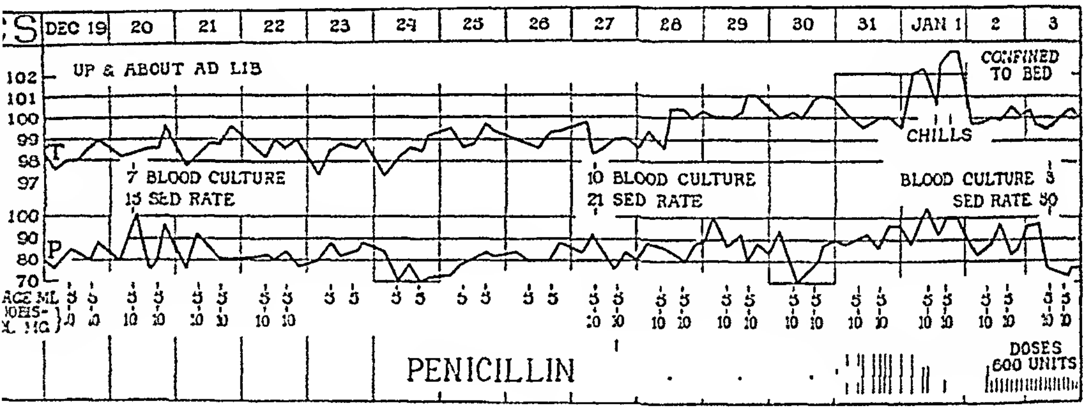

Fig. 2.

On December 3, the erythrocyte sedimentation rate was 29 mm. in an hour; the blood pressure was 128/71. A blood culture taken at this time was reported as unsatisfactory and of doubtful significance because of the growth in it of staphylococci which were considered to be contaminants. The diagnosis of staphylococcal endocarditis was not accepted as fully established. Nevertheless, a stock staphylococcus bacteriophage was administered by intravenous injection twice daily, and thiobismol was also given. The patient was confined strictly to bed until December 10, and then was allowed to be up and about until January 1. During this period, the diagnosis of staphylococcemia became established by consistently positive blood cultures taken by meticulous technique on December 6, 13, 20, and 27. The patient had been referred with the hope that he might be treated with penicillin, and he became progressively discouraged.

The penicillin which became available on December 27 was a partially purified preparation in phosphate buffer solution. It evidently contained considerable amounts of pyrogenic impurities. Intramuscular

APPARENT ARREST OF STAPHYLOCOCCAL ENDOCARDITIS

Ward J. MacNeal, M.D., Charles A. Poindexter, M.D., New York, N. Y., and Frederick N. Marty, M.D., Syracuse, N. Y.

C. S., a white man, born April 5, 1907, gave a history of "kidney trouble" in 1924, for which he took a milk diet for some time. About 1932 he had a typical attack of rheumatic fever, with severe pain and swelling and tenderness in the hips, knees, and ankles. During this illness he had an acute middle ear infection. A myringotomy was performed, and thereafter he had a persistent hearing defect in his right ear. After this attack of rheumatic fever, tonsillectomy was performed. There was no recognized recurrence of rheumatic fever. During the summer of 1943, while engaged as a superintending engineer of construction work in Tennessee, he suffered from chigger bites on his lower extremities, and one of these lesions suppurated for several weeks. In October, 1943, he returned to his home in Syracuse, New York, for a short vacation.

He consulted his local physician (F. N. M.) on October 20, stating that he had felt well until the previous three or four days, when he noted soreness in the calves of both legs and lameness in his left shoulder. He also had pains in the back of his neck and an occasional headache. He had not had weakness, dyspnea, chest pain, cardiac palpitation, undue fatigue, ankle edema, or any sensation of chills and fever.

The patient was a well-developed and well-nourished man of athletic build. His temperature, as observed at home for several days, was no higher than 99.8° at any time. An aortic diastolic murmur and a loud, rough, systolic, blowing murmur were heard over the precordium, and the heart was moderately enlarged. The leucocyte count was 9,300, with 73 per cent polymorphonuclears and 27 per cent lymphocytes. The sedimentation rate was 30 mm. in an hour (Cutler method). Examination of the urine was negative. He was sent home to bed with a provisional diagnosis of mild recurrent rheumatic fever.

After three or four days of rest in bed. his previous complaints disappeared entirely. He was suddenly seized, however, with sharp pain in the lower right quadrant of the abdomen, just a little to the right of the midline. Several total and differential leucocyte counts, as well as urinalysis, were done, and failed to reveal evidence of any acute inflammatory process. A local surgeon saw him in consultation at this time, but, after several days of rest in bed, the pain subsided completely. A blood culture taken Oct. 22, 1943, revealed *Staphylococcus aureus,* and blood cultures were repeated at intervals of a week until three had been taken; all were positive for *Staph. aureus.*

On Nov. 16, 1943, he was admitted to the Syracuse Memorial Hospital for further observation and treatment with large doses of sulfadiazine. He was given this drug in doses of 1.5 Gm. every four hours for five

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Aided in part by Grants No. 500 and No. 501 of the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association.

The penicillin used was generously supplied by Rare Chemicals, Inc., Flemington, N. J., and by Chas. Pfizer, Inc., Brooklyn, N. Y.

Received for publication Sept. 13, 1944.

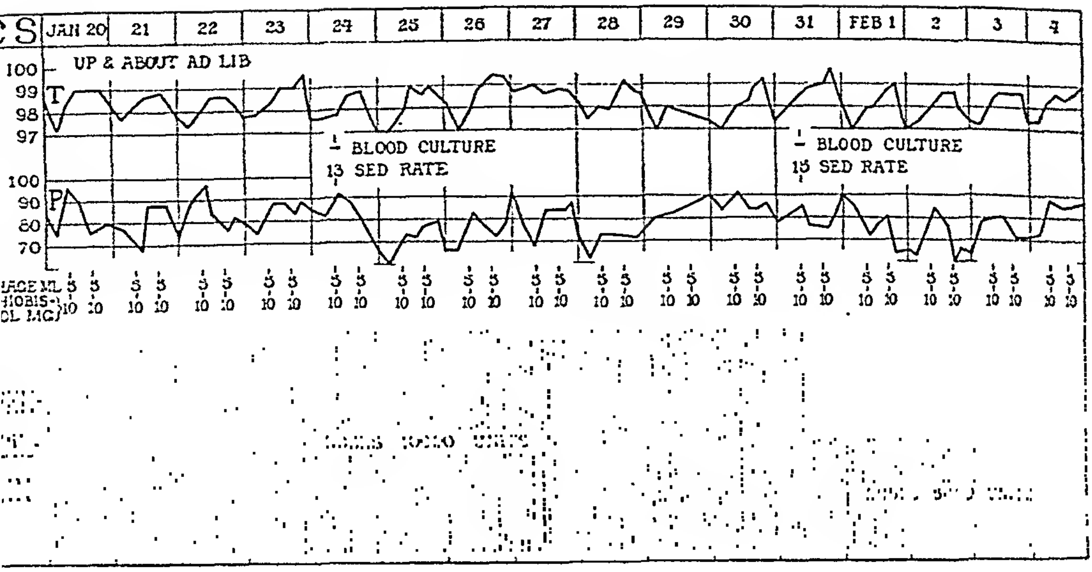

Fig. 4.

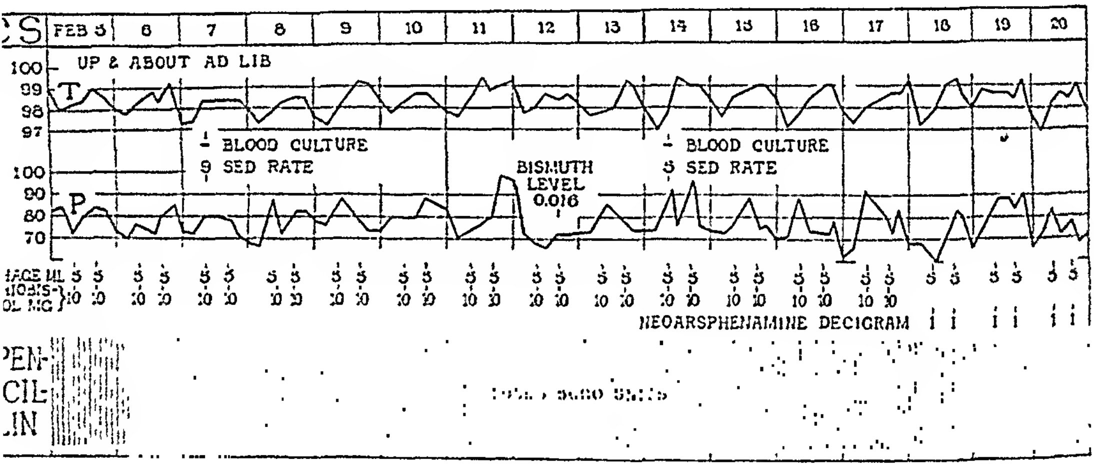

Fig. 5.

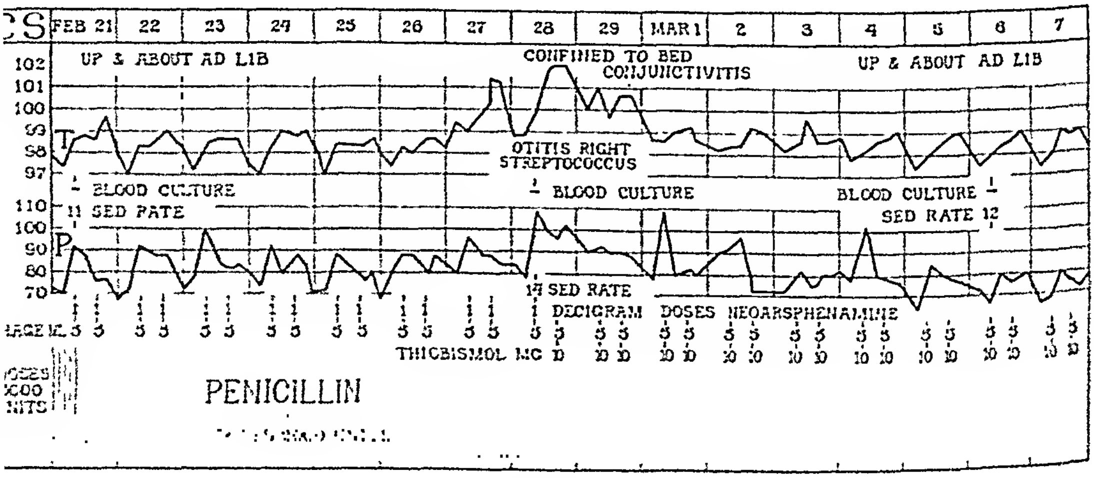

Fig. 6

injections of approximately 1,800 units every two hours caused pain at the injection sites, and, on December 31, the patient was no longer willing or able to accept the treatment. The chills and rise in temperature on January 1 were ascribed to the action of this preparation of penicillin. Subsequently, doses of 600 units were accepted without too much complaint, but the patient felt that he was not improving under this treatment.

On January 9 a supply of refined penicillin became available, and this was injected intravenously during the day and intramuscularly at night in doses of 5,000 units every two hours from January 9 to 18. The blood culture on January 10 showed a growth of less than one colony per milliliter of blood, and all the subsequent cultures, of which there were many, remained negative. The sedimentation rate was 50 mm. on January 3, 30 mm. on January 10, and 28 mm. on January 17. Encouraged by these signs of improvement, we continued the bacteriophage and the thiobismol, and, on January 18, increased the penicillin dose to 10,000 units every two hours and continued this dose to January 31.

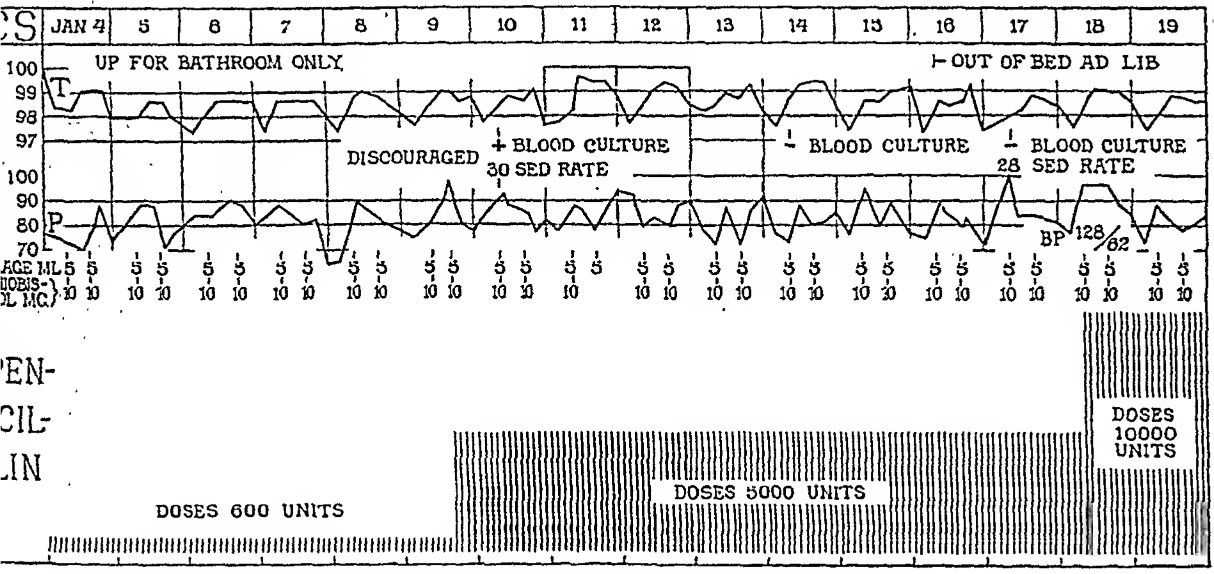

Fig. 3.

The penicillin dose, for sake of economy, was then reduced to 5,000 units every two hours from January 31 to February 21. From February 18 to 28 the thiobismol was omitted, and neoarsphenamine was administered in a dose of 10 mg. twice a day. On February 28 the thiobismol was resumed. The dose of penicillin was reduced on February 21 to 2,000 units every two hours, and finally discontinued altogether on February 28. The injections of staphylococcus bacteriophage and thiobismol were continued to March 18, when the patient was discharged from the hospital, and the injections of the bacteriophage were still being continued when this report was written (September, 1944). It will be noted that the sedimentation rate did not exceed 15 mm. per hour after January 17, and that the blood cultures remained consistently negative.

The changes in the cardiac murmur were of clinical interest, and probably of considerable significance for the diagnosis. During December there was a double mitral murmur of blowing quality, diastolic and systolic, transmitted to the left axilla. On January 18 the systolic murmur had become more loud and harsh, and was best heard at a point 2 cm. below the left nipple. This harsh sound occurred in late systole,

April 5, April 10, May 4, June 7, July 6, August 3, and August 8 have remained sterile. The patient has gained in strength and weight. He is now back at work.

The significant data on the blood counts are shown in Table I. No transfusions were required. Routine examinations of the urine, made weekly, revealed nothing abnormal.

CONCLUSION

We recognize that a diagnosis of staphylococcal mitral endocarditis may be disputed in the absence of an anatomic and cultural study of the cardiac valves themselves. Nevertheless, it is our considered opinion that this patient* actually suffered from bacterial mitral endocarditis caused by infection with *Staphylococcus aureus*, and that the disease is now in a stage of arrest, which may possibly be permanent.

*The patient was still in excellent condition, with a persistent mitral murmur, on Jan. 11, 1945.

and was designated by different observers as a "leathery squeak," a "late systolic bleat," and "whistling character of murmur." In the axilla the systolic murmur continued to have the earlier blowing quality. After February 1, this curious squeaky murmur became less and less perceptible. The blowing double mitral murmur persisted.

The discouraging upset which began on February 26 was evidently related to an exacerbation of the old otitis media. From the exudate from the auditory canal both a streptococcus and staphylococcus were cultured. The inflammation subsided after irrigation, and the general therapeutic program was not disturbed on this account.

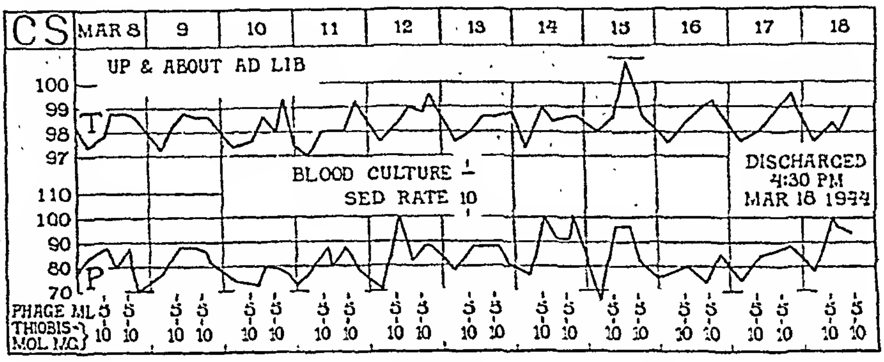

Fig. 7.

After his discharge from the hospital, on March 18, the patient remained in New York for several weeks, and was treated daily with intravenous injections of bacteriophage. He then went to his home in Syracuse, where he has been treated by Dr. Marty. He has since returned to New York City several times for physical examination, leucocyte count, blood culture, and sedimentation rate. The results of these tests have been satisfactory. The sedimentation rate in millimeters per hour was 9 on April 3; 7 on April 10; 8 on May 4; 7 on June 7; 7 on July 6; 8 on August 3; and 5 on August 8. Blood cultures taken

TABLE I

ABRIDGED DATA OF ROUTINE EXAMINATION OF BLOOD

DATE	ERYTHROCYTES (×1,000)	HEMOGLOBIN (GM.)	LEUCOCYTES	NEUTROPHILES (%)	EOSINOPHILES (%)
Dec. 4	4,400	14.5	10,050	75.5	2.0
Dec. 13	4,680	15.0	9,000	62.0	3.0
Dec. 27	4,040	12.7	8,350	70.0	3.0
Jan. 3	5,090	14.0	7,200	59.0	6.0
Jan. 10	5,330	14.0	11,650	69.0	2.0
Jan. 18	5,430	14.0	14,150	77.0	1.0
Jan. 24	5,490	15.0	9,350	67.0	2.0
Jan. 31	5,790	15.8	7,800	64.0	6.0
Feb. 7	4,470	13.5	10,250	67.0	3.0
Feb. 14	4,610	13.6	7,350	71.0	2.0
Feb. 21	4,870	14.5	7,300	62.0	6.0
Feb. 28	5,570	14.8	6,450	76.0	3.0
Mar. 6	5,020	15.0	7,050	68.0	6.0
Mar. 13	4,720	13.5	8,850	64.0	7.0
May 4	4,740	14.0	11,250	59.0	3.0
June 7	5,000	15.0	9,950	57.0	1.0
July 6	5,060	16.0	10,400	63.0	2.0

Sharpey-Schafer, E. P.: Cardiac Output in Severe Anaemia. Clin. Sc. 5: 125, 1944.

This paper reports results obtained in posthemorrhagic and chronic anemia including some cases showing evidence of congenital heart failure for which no cause other than anemia was discovered. The author used a method of cardiac catheterization as a means for determining cardiac output and by the same method was able to measure directly the mean right auricular pressure and percentage of utilization of available oxygen.

Resting minute oxygen consumption was not reduced in chronic and posthemorrhagic anemia. Oxygen supply was maintained by increased cardiac output which at the lowest hemoglobin levels approximated the minimum necessary output, increased removal of oxygen in the periphery (up to 90 per cent of available oxygen), and reduced blood volume, resulting in greater concentration of total hemoglobin.

Venous pressure is increased in the most severe cases. This congestive heart failure in anemia was associated with increased cardiac output and decreased blood volume. Passive venous congestion *will not explain these findings and conspicuous* increase of venous pressure may represent the last stage of a process of adjustment, which maintains the necessary minute output.

The phase of increased cardiac output and pulse pressure after hemorrhage did not develop immediately and was preceded in three cases by a phase of low blood pressure and probably reduced cardiac output.

AUTHOR.

Berconsky, I.: Preventive Treatment of Supraventricular Paroxysmal Tachycardia With Carbamilcolina. Rev. argent. de cardiol. 11: 120, 1944.

Carbaminoylcholine chloride (Carbachol), in doses of 4 mg. per day, was used as a preventive of attacks of supraventricular paroxysmal tachycardia. In four patients with frequent crisis, this treatment prevented the attacks where quinidine and digitalis had previously failed.

AUTHOR.

Dubin, I. N., and Hollinshead, W. H.: Congenitally Insufficient Tricuspid Valve Accompanied by an Anomalous Septum in the Right Atrium. Arch. Path. 38: 225, 1944.

In tho case described the tricuspid insufficiency apparently resulted from lack of differentiation of the tricuspid valve, hypoplasia of the papillary muscles and aplasia of most of the chordae tendineae. The heart contained a large anomalous septum in tho right atrium, probably representing a persistent right valve of the sinus venosus.

AUTHORS.

Shapire, M. J.: Preoperative Diagnosis of Patent Ductus Arteriosus. J. A. M. A. 126: 934, 1944.

Rickettsial spotted fever is a severe systemic disease. It is rarely diagnosed until the skin rash has appeared. No specific therapeutic agent is available which is effective after the third day of the rash; hence, therapy must be largely supportive.

Regulation of supportive therapy, based on tho pathologic physiology of the disease, has not been attempted. Because of the vascular lesions, the loss of circulating body fluids, particularly protein, is analogous to that in burns, and peripheral circulatory collapse may develop if inadequate or improper treatment is given. The administration of saline solution or glucose without blood or plasma will aggravate, rather than correct, the abnormal physiology by washing out further protein.

Abstracts and Reviews

Selected Abstracts

Crismon, J. M.: Effect of Hypothermia on the Heart Rate, the Arterial Pressure and the Electrocardiogram of the Rat. Arch. Int. Med. 74: 235, 1944.

The effects of hypothermia on the heart rate, the arterial pressure, and the electrocardiogram of rats cooled to lethal levels were investigated.

Both the heart rate and the conduction of the cardiac impulse were slowed by reduction of the body temperature. The relationship of the heart rate to the body temperature was linear over the range from 15° to 35° C. (59° to 95° F.), with a Q_{10} of 2.14, and had a high positive correlation. The slowing of conduction in the heart was proprtional to the change in heart rate.

During the reduction of body temperature, the arterial pressure increased as the shivering became maximal down to a rectal temperature of 29° C. (84.2° F.). Further reduction of temperature resulted in a decline of arterial pressure, at first gradual, until the temperature reached about 23° C. (73.4° F.), and then precipitous, as the temperature fell below 21° C. (69.8° F.). The relation between arterial pressure and heart rate became linear after the heart had slowed to about one-third the normal rate. Complete atrioventricular block was observed only after the arterial pressure had reached levels below 80 mm. of mercury.

Abnormalities of the P wave and complete atrioventricular dissociation were the most striking features at low temperatures. The arrhythmias were of two types: sinoatrial block with shift of the pacemaker to other parts of the atria and finally the establishment of atrioventricular nodal rhythm and complete atrioventricular block. The first type was reversible by raising the body temperature slowly; the second may be corrected by administering artificial respiration, or may disappear when the temperature rises slowly during recovery.

Respiratory arrest in hypothermic rats occurred only after the arterial pressure had fallen below 70 mm. of mercury. The circulatory failure preceding respiratory arrest was closely related to the degree of cardiac slowing.

AUTHOR.

Member, S., Bruger, M., and Oppenheim, E.: Experimental Atherosclerosis. Arch. Path. 38: 210, 1944.

Cholic or glycocholic acid fed with cholesterol to the rabbit increases markedly the cholesterol contents of the whole blood and the aorta as compared with the levels obtained following the ingestion of cholesterol alone.

Dehydrocholic acid, hyodesoxycholic acid, and desoxycholic acid do not possess this property.

In two series of experiments in which desoxycholic acid and glycocholic acid were used, respectively, the latter was shown to augment the cholesterol content of the liver; the former was without effect in this regard.

The feeding of cholic acid, unlike that of any other bile acid tested, is accompanied by increased concentration of combined (ester) cholesterol in the whole blood.

AUTHORS.

incidence of positive cutaneous reaction in the normal siblings of these rheumatic children is the same as in rheumatic children.

The cutaneous reactions of normal children are of a significantly milder degree than those of rheumatic children and their siblings; the highest degree of reactivity was found in the normal siblings of rheumatic children.

The incidence and the degree of cutaneous reaction to the M fraction of the hemolytic streptococcus are not influenced by the age of the child, between the ages of 6 and 16 years, or by the rheumatic status; active cases do not show a higher incidence or degree of cutaneous reactivity.

Cutaneous reactivity to specific M fraction in rheumatic children diminishes only slightly with the lapse of time following an acute rheumatic episode.

AUTHORS.

Mendelson, C. L.: Management of Delivery in Pregnancy Complicated by Serious Rheumatic Heart Disease. Am. J. Obst. & Gynec. 48: 329, 1944.

The successful management of pregnancy complicated by serious rheumatic heart disease requires a program of medical and surgical obstetrics of the highest order. Barring other obstetric complications, the vast majority of cases can be successfully delivered by the vaginal route. When indicated, vaginal therapeutic abortion is a relatively safe procedure for interruption of early pregnancy.

The hazards of labor can be definitely reduced with good ante-partum care, careful functional evaluation, adequate digitalization, and shortening of the second stage. The pulse and respiratory rates intrapartum provide a valuable guide to the cardiac status. Abdominal delivery has been performed with decreasing frequency, and yet it may still have its place in those patients who fail to improve in spite of treatment. Each patient should be evaluated as an individual problem. Once severe cardiac failure has occurred ante partum, there is a great risk in discharging the patient from the hospital before delivery.

The incidence of spontaneous abortion and premature labor, the duration of labor, and the blood loss at parturition in women with serious rheumatic heart disease are not significantly different from values in normal women.

AUTHOR.

Salit, E. P., and Tuttle, W. W.: The Variability of Heart Rate and Blood Pressure in Selected Groups of College and High School Students. J. Lab. & Clin. Med. 29: 1139, 1944.

Pulse after a standard exercise is a more reliable measure than the resting pulse, but the resting systolic blood pressure is a more reliable measure than the systolic pressure after exercise.

Even when conditions are carefully controlled, an individual's heart rate and blood pressure are so variable from day to day that a number of determinations must be made if his general status is to be established.

Cardiovascular tests in general have little discriminatory power because the differences in scores among individuals are small in relation to individual variability.

Individuals can more clearly be distinguished from each other on the basis of postexercise pulse rates than on the basis of resting heart rate or the increase due to moderate exercise. The same is true of postexercise systolic and diastolic blood pressures.

The relative efficiency of heart rate scores in distinguishing individuals from each other has been demonstrated in terms of the percentage of significant differences among individuals in a group. Whereas only 8 per cent of the differences in the resting pulse for the twenty men in our experiment are significant at the 1 per cent level of confidence, 41 per cent of the differences in pulse one-half minute after exercise are significant at this level. The corresponding figures for the women

Intravenous therapy, properly chosen, is not harmful, as it has been reported to be, but may prove lifesaving. It should include plasma and whole blood in adequate quantities in addition to glucose, salts, vitamins, and amino acids. Careful laboratory control in choosing the type and quantity of parenteral or oral fluids to be administered is important.

The elevation of the blood nonprotein nitrogen and lowering of blood chlorides are connectable.

Edema of the subcutaneous tissues and lungs can be produced by excessive administration of crystalloids. The increase in water binding power of the circulating fluid, produced by the administration of blood and plasma, pulls water out of the interstitial spaces and reduces the edema. The peripheral circulation can be supported and the blood pressure raised from shock levels.

The serum proteins are produced; nitrogen excretion studies suggest that protein destruction is great. The impairment of liver function makes protein replacement therapy necessary for variable lengths of time.

AUTHOR.

Coulter, W. W., and Marcuse, P.: Acute Isolated Myocarditis. Am. J. Clin. Path. 14: 399, 1944.

A case is reported in which a nonspecific type of myocarditis and less marked nonspecific changes in the lungs and liver were the pathologic findings. The lesions in the heart muscles were severe enough to account for the patient's sudden death after a short illness with vague symptoms.

AUTHORS.

Waitzkin, L.: Impending Myocardial Infarction. Ann. Int. Med. 21: 421, 1944.

Acute myocardial infarction is preceded by premonitory symptoms in a goodly percentage of cases. In a patient previously well, cardiac pain, however brief and mild, suddenly appearing during rest or customary activity, may imply existing or imminent myocardial infarction. In a case of pre-existing angina pectoris, cardiac pain, more readily precipitated by effort or beginning to occur at rest, may imply existing or imminent myocardial infarction. In considering symptoms suspected as premonitory it must be recognized that myocardial infarction does not inevitably follow them, but the strong possibility that it may should lead to heightened suspicion and therapeutic precautions.

AUTHOR.

Pease, P. P., Steuer, L. G., and Peters, C. H.: Value of the Electrocardiogram in Acute Rheumatic Fever. Mil. Surgeon 95: 287, 1944.

The value of routine serial electrocardiograms in acute rheumatic fever has again been pointed out. Three cases are reported showing electrocardiographic evidence of cardiac damage which might have otherwise escaped detection.

AUTHORS.

Taran, L. M., Jablon, J. M., and Weyr, H. N.: Immunologic Studies in Rheumatic Fever. I. Cutaneous Response to Type-Specific Proteins of the Hemolytic Streptococcus. A. Response to Combinations of "M" Proteins From Selected Types of Hemolytic Streptococci. J. Immunol. 49: 209, 1944.

Cutaneous reaction to the M fraction of twenty-five known Griffith types of hemolytic streptococcus was studied in rheumatic children, their normal siblings, and normal children. The incidence of positive cutaneous reaction in normal children is 65 per cent as compared with 83 per cent in rheumatic children. The

To determine whether or not a toxin may have developed in the constricted limb and may have been an important factor in the pathogenesis of shock and death, we performed cross transfusion, injecting blood obtained from the distal portion of the femoral vein of the constricted limb into a normal (control) animal. To prevent increase in shock in the animal subjected to the application of the tourniquet through loss of blood, an equal amount of blood was removed from the recipient (control) animal, and injected into the shocked animal.

Because of exigencies of war, work on the problem was interrupted; only five such experiments could be performed. Four of the five animals receiving blood from the constricted limb after release of the tourniquet died two to twelve hours after the transfusion was begun. The only dog to survive transfusion of blood which had circulated through the contricted limb was one which did not receive any blood from the constricted limb until ten minutes following release of the tourniquet. If a toxin were present in the constricted limb it would supposedly be more concentrated in the blood draining from the limb during the first few minutes following release of the tourniquet. If this were true, survival of this animal, which, however, did go into shock during the transfusion (but recovered afterward), might be explained.

AUTHORS.

Joselevich, M., and Mactas, B. A.: **Radiologic Image of the Arch of the Azygos Vein in Cardiovascular Disease.** Rev. argent. de cardiol. 11: 98, 1944.

Out of 1,287 chest x-ray films of ambulatory patients, one hundred ninety per cent (15 per cent) showed the right paratracheal image corresponding to the normal course of the arch of the azygos vein and seven (5.4 per cent) showed the presence of the Wrisberg's lobe.

The x-ray films were classified in six groups according to the clinical diagnosis of the patients: various noncardiac; pulmonary; rheumatic fever; heart disease, compensated; arterial disease, compensated; cardiac insufficiency.

The paratracheal images were classified according to size in two types: with longitudinal and transverse diameters of less than 15 and 5 mm., respectively, and with diameters greater than these. Images of both were found in a proportion of 83.9 and 16.1 per cent, respectively, in patients of the first mentioned group; of 65 and 35 per cent in those of the second group; of 66.6 and 33.3 per cent in patients of the fourth group; of 58.1 and 41.8 per cent in those of the fifth group; and of 30 and 70 per cent, respectively, in patients of the last group.

Of the fourteen images of the second size found in the group of noncardiac patients, seven corresponded to pregnant women and three to hyperthyroids. Of twelve patients with cirrhosis, five showed the paratracheal image: three of the first size and two of the second size.

Our results tend to confirm the findings of others which showed an increase in size of the paratracheal image in cardiac insufficiency, in hyperthyroidism (in both cases due probably to a high venous pressure), and in cirrhosis of the veins. The same finding was made in the seven cases of Wrisberg's lobe, showing that the arch of the anomalous azygos vein responds as the normal to the causes which determine the increase of its radiological shadow.

AUTHORS.

Sherman, C. F., and Ducey, E. F.: **Cardiac Mensuration.** Am. J. Roentgenol. 51: 439, 1944.

A direct comparison was made between the transverse cardiac diameter of two hundred adult males, obtained within ninety days of death, and the weight of their hearts at autopsy.

In this study, the results by the Ungerleider method are much more closely correlated with the actual cardiac weight than are those of the other two roentgen methods studied.

are 25 per cent and 32 per cent. At the 5 per cent level of confidence, 62 per cent of the differences in pulse after exercise are significant among the men; among the women only 53 per cent of the differences are significant at this level of confidence.

AUTHORS.

Webb, A. C.: Periarteritis Nodosa in Pregnancy. Arch. Path. 38: 329, 1944.

Periarteritis nodosa was observed in a parturient woman whose death most probably can be ascribed to severe toxemia and puerperal sepsis. The role played by the lesions of periarteritis nodosa in relation to the death of the patient cannot be evaluated.

AUTHOR.

Hines, E. A., Jr.: The Prevention of Venous Thrombosis and Pulmonary Embolism. J. South Carolina M. A. 40: 159, 1944.

Some of the general measures which may be of help in the prevention of postoperative venous thrombosis and pulmonary embolism are: careful surgical technique with avoidance of trauma to tissue and especially to blood vessels; the preoperative and postoperative treatment of anemia; avoidance of abdominal compression by tight compresses and bandages; adequate fluid intake; prompt treatment of infection; warm environmental temperatures, especially about the lower extremities; respiratory and leg exercises and massage; and keeping the patient in bed for as short a period as practicable.

The author also discusses the special methods used for the prevention of anticoagulant therapy and ligation and division of the femoral and iliac veins and thrombectomy. It is his opinion that the operative procedure is less safe and more conducive to permanent chronic venous insufficiency than is adequate and properly controlled anticoagulant therapy.

AUTHOR.

Chess, S., Chess, D., and Cole, W. H.: Experimental Tourniquet Shock With Particular Reference to the Toxic Factor. A Method of Production Eliminating the Influence of General Anesthesia and Nervous Impulses. Arch. Surg. 49: 147, 1944.

Tourniquet shock can be produced consistently in animals and is therefore particularly adaptable for study, but the extreme pain produced by the tourniquet makes it necessary to utilize some type of anesthesia. Prolonged anesthesia, whether produced by a barbital compound or a general anesthetic, is undesirable. Moreover, since nervous impulses are obviously so intensive, this factor might alter the data derived from the experiment. To obviate these disadvantages we have adopted the procedure of cutting the spinal cord at the level of the lowest dorsal or the uppermost lumbar vertebra, two to four days before the experiment is to be performed. It is unwise to wait much longer, since the anesthesia induced in the lower extremities, which are dragged over the floor of the cage, may allow development of ulcers, infection, etc. Manipulation or operation may be conducted without pain on the lower extremities of the animal with no more anesthetic than a moderate dose of morphine. To keep the tourniquet anchored in one place a sterile nail can be driven deeply into the trochanter. In the experiments in which shock was produced by release of the tourniquet, death always occurred if the tourniquet had been left in place for at least nine hours. In ten animals studied by this method, death occurred after an average of two hours and thirty-four minutes following release of the tourniquet. The average loss of plasma into the extremity before and following release of the tourniquet, as determined by the method of Blalock, was only 2.1 per cent of the total body weight, which is insufficient in itself to explain death.

A case is reported of aneurysm of the renal artery associated with calculus pyonephrosis, in which a correct preoperative diagnosis was made by finding a typical ring shadow on the x-ray film in the region of the renal pelvis. Owing to the location of the aneurysm, the lesion was missed at operation, but was clearly disclosed on pathologic examination of the extirpated kidney.

AUTHORS.

Yonkman, F. F.: Toxicity of Yohimbine Hydrochloride. J. Lab. & Clin. Med. 29: 1222, 1944.

Yohimbine, fed ad libitum to rats in drinking water, seems to be nontoxic for over three months except when the concentration in the water is increased to 1:1,000. On higher dilutions, growth and vigor are generally maintained at good levels and habits are normal. Autopsy findings are essentially normal.

AUTHOR.

Quick, A. J.: Anitcoagulants Effective in Vivo With Special Reference to Heparin and Dicumarol. Physiol. Rev. 24: 297, 1944.

The normal antithrombin of the blood is closely associated with the albumin fraction. It does not inhibit or retard coagulation, but merely inactivates thrombin. Quantitative methods have been developed for its determination, but the significance of its variation in the blood remains obscure.

Heparin, the natural physiologic anticoagulant, is a compound closely related to mucoitin-polysulfuric acid. Due to its strongly acidic character, it forms complexes with various proteins and other biologic compounds. Heparin per se is not an antithrombin, but with a cofactor present in serum albumin forms a strong thrombin-inactivating complex. Heparin in inhibiting the conversion of prothrombin to thrombin likewise requires a cofactor which is present in the plasma. Heparin prevents the agglutination of platelets, probably by virtue of its anticoagulant action. The function of heparin in the body has not been determined. It is liberated during anaphylactic and peptone shock, but the mechanism whereby this is brought about is still obscure, and the purpose of this physiologic response has not been ascertained.

Antithromboplastin has been demonstrated in the blood, and evidence has been found that it is abnormally increased in hemophilic blood.

Dicumarol is the toxic principle isolated from spoiled sweet clover hay. It is a coumarin derivative which had not hitherto been known to occur in plants. When dicumarol is administered orally or intravenously to man or animals, it causes a gradual but severe decrease of the prothrombin of the blood (or more accurately of component B of prothrombin). Several days are required for the production of its full effect, and recovery is equally slow. Evidence is accumulating which suggests that vitamin K has some antagonistic action against dicumarol. The hypoprothrombinemia produced by the drug can be temporarily alleviated by transfusion. Dicumarol appears to have no toxic action other than depressing the prothrombin except in excessive dosage. It is probable that some of the pathologic findings in fatal cases of dicumarol poisoning can be attributed to tissue anoxia due to the severe anemia after excessive hemorrhage.

Salicylates especially when given to animals on a low vitamin K diet depress the prothrombin of the blood but to a much smaller degree than dicumarol. Sulfaguanidine and succinylsulfathiazol also cause a hypoprothrombinemia, but the action appears to be due to a depression of the synthesis of vitamin K by the bacteria of the intestines and not to a direct action on the synthesis of prothrombin.

AUTHOR.

There is constant correlation between the percentage deviation of the transverse diameter, as obtained by the Ungerleider method, and the percentage deviation in heart weight as calculated from Zeek's table. This correlation expressed numerically has a value of 1:3.3.

Marked deviation from normal body weight and pericardial effusion greater than 200 c.c. impair the accuracy of the method to such an extent as to preclude its use without qualification.

AUTHORS.

Monahan, D. T.: Ligation of the Aorta and Both Common Iliacs for Aneurysm. Surgery 16: 519, 1944.

A case is reported in which the aorta was occluded in stages by rubber bands proximal to an aneurysm with division of both common iliac arteries. The patient lived approximately five months from the time of the first ligation. Seven cases of aortic ligation are reviewed. Of these, there were four partial, and three total, occlusions. Of the three total occlusions, two patients had collateral established at the time of operation, and the third had alarming paralysis of the extremities following ligation, and survived probably because of his youth.

Occlusion of the lower abdominal aorta is feasible. Furthermore, man will tolerate division of both common iliacs after ligation of the aorta. Cotton tape has been demonstrated as the least noxious material for ligation. It seems reasonable that ligation in stages with cotton tape, plus ligation of both iliacs, should cure aneurysms of the lower abdominal aorta.

AUTHOR.

Lazarus, J. A., and Marks, M. S.: Aneurysm of the Renal Artery—True and False—With Special Reference to Preoperative Diagnosis. J. Urol. 52: 199, 1944.

Aneurysm of the renal artery is a rare clinical entity, as evidenced by the fact that we were able to collect only seventy-five cases from the literature. This includes the case here presented.

A history of trauma was elicited in 34.7 per cent of these cases. Among the other etiological factors associated with this condition are systemic debilitating infections and atherosclerosis.

Pathologically, aneurysms may be classified as (a) true and (b) false. True aneurysm is a saccular dilatation of an artery containing all the elements of the arterial wall and results from weakening of the arterial wall as a result of sclerosis, fatty degeneration involving the elastic fibers from some debilitating systemic infection, or atherosclerosis. A false aneurysm is a saccular dilatation of an artery due to trauma resulting in complete disruption of continuity of the arterial wall either in part or in its entirety, in which the limiting walls from without inward consist of adventitia, laminated blood clot, and endothelium.

Small aneurysms of the renal artery usually give rise to no symptoms. Larger aneurysms, however, usually give rise to symptoms, the most common of which is pain in the loin (62.7 per cent). A mass was felt in the loin in 30 per cent of the recorded cases.

The presence of an opaque ring shadow with dense periphery on the x-ray film in the region of the renal pelvis is an extremely valuable diagnostic sign of this disease.

The indicated procedure in the treatment of renal artery aneurysm is immediate nephrectomy with ligation of the renal artery proximal to the point of origin of the aneurysm.

American Heart Association, Inc.

1790 Broadway at 58th Street, New York, N. Y.

The American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The American Heart Journal is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

Annual membership is $5.00. Journal membership at $11.00 includes a year's subscription to the American Heart Journal (January-December) and annual membership in the Association. The Journal alone is $10.00 per year.

The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

**Executive Committee.*

Book Reviews

Clinical Heart Disease: By Samuel A. Levine, M.D., Assistant Professor of Medicine, Harvard Medical School. Ed. 3, W. B. Saunders Company, Philadelphia, 1945, 462 pages, 157 illustrations, $6.00.

The author states that the general character of the book has not been changed from that of previous editions. The discussion of the surgical treatment of patent ductus arteriosus and of the chemotherapy of subacute bacterial endocarditis has been amplified, the latter to include penicillin. Brief reviews of scleroderma heart, rupture of valves, and the heart in Addison's disease have been added. The discussion of electrocardiography has been elaborated. A few phonocardiograms are reproduced in this edition.

The book is intended for the general practitioner. Its popularity is attested by the frequency with which new editions appear. The subject matter is presented in clear and simple form and, in general, reflects the most widely accepted views. The author seems to be at his best when he discusses treatment, although the part of the presentation of electrocardiography dealing with abnormal cardiac mechanisms is also very well done. He belongs to the school of thought which holds that, as a rule, only one chest lead, in addition to limb leads, is necessary for the study of myocardial damage, although he does concede that, in case of doubt, three or six chest leads may be useful. Like most authors of books on the heart, he does not appear to be troubled by doubt as to the complete validity of the Einthoven equilateral triangle hypothesis and all the tidy concepts erected upon it.

Charles C. Wolferth.

Erratum

In the article entitled "The Effect on the Blood Pressure of Normal Persons and Hypertensive Patients of Glyceryl Trinitrate, Sodium Nitrite, Erythrol Tetranitrate, and Mannitol Hexanitrate," by John C. Weaver, J. H. Wills, and H. C. Hodge, which appeared in the November, 1944, issue of the Journal, volume 28, page 603, the dose of nitroglycerin, given in the second line of the first paragraph, should read 0.0006 Gm. instead of 0.006 Gm.

Thomas Lewis
1881-1945

of physiology, normal and abnormal, in animals and in man, helped by the application of the experimental method, was the keynote of Thomas Lewis' scientific life. It happened through Mackenzie's influence that the circulatory system was his special field of interest, but he preached the gospel of his high standards of scientific endeavor to all workers in clinical medicine in order to raise up a group of vigorous investigators in what he called clinical science. He passed on the torch which he had carried for years, beginning in 1909, the date of the first issue of the journal *Heart*, to the editors of *Clinical Science* (incorporating *Heart*) in 1933. His emphasis was on the study of man himself.

In the course of his studies he made many contributions of value and several of lasting note. He described auricular fibrillation in man in 1909, the spread of the electrical impulse in the mammalian heart over a period of a number of years following that date, the characteristics of the various arrhythmias and their responses to various drugs, peripheral vascular disorders, the reactions of the blood vessels of the skin, and the mechanism of pain. He wrote important books at a young age, his most notable being his masterpiece, the *Mechanism of the Heart Beat,* in 1911, when he was only 29. This volume he enlarged considerably in two later editions which he called *The Mechanism and Graphic Registration of the Heart Beat,* the third being published in 1925. He wrote voluminously but always to the point without waste of words.

Among his other more important books were those on *The Soldier's Heart and the Effort Syndrome* (first edition, 1918, second edition, 1940), *Blood Vessels of the Human Skin and Their Responses* (1927), *Vascular Disorders of the Limbs* (1936), and *Pain* (1942). He assembled his experience and ideas about *Heart Disease* in a small volume in 1932 (second edition, 1937) and he prepared small guidebooks for the clinician, summarizing the current knowledge of the arrhythmias assembled by Mackenzie, Wenckebach, himself, and others, entitled *Clinical Disorders of the Heart Beat* (first edition, 1912; sixth edition, 1926), and of electrocardiography in the early days entitled *Clinical Electrocardiography* (first edition, 1913; sixth edition, 1937). *Lectures on the Heart,* published in 1915, comprised the series of special talks that he gave in the United States on one of his visits to this country.

But more important than his writings was his influence on his students and associates and on the medical thought of his time. His was a forceful, keen intellect, brooking no deceit, laziness, or sluggish inaccurate thinking or writing. He was very economical in his own speech and intolerant of verbosity in others. His thoughts usually leaped ahead of those of the people about him, and in his earlier years he expressed his impatience often forcefully—it was a waste of his valuable time, he seemed to imply, to have to explain things over and over. As he grew older he became more tolerant of the shortcomings of others and of the contributions that others were making, but his earlier attitude was a powerful stimulus to those of his students who could weather the strain, to emulate his industry, initiative, and accuracy.

Among his many students were young American physicians who, at the present day, may be found in the larger medical centers of this country at the peaks of their useful careers in medicine, particularly in their chosen field of cardiology, and who gratefully acknowledge the debt they owe to the great master. It is therefore particularly appropriate for the American Heart Association through its JOURNAL to render herewith its homage to the memory of Thomas Lewis.

PAUL D. WHITE.

American Heart Journal

VOL. 29 APRIL, 1945 NO. 4

In Memoriam

THOMAS LEWIS

1881-1945

The world has lost a great medical leader. Thomas Lewis died at his home in Rickmansworth, England, on March 17, 1945, in his sixty-fourth year, after a fourth attack of myocardial infarction, the first illness of the sort having occurred eighteen years earlier. Like his own master, James Mackenzie, he suffered from a disease of the circulation, but despite it, made some of his most important contributions after the onset of this trouble.

Thomas Lewis was born in Wales in 1881, the son of Henry Lewis of Cardiff. He received his collegiate and professional education at the University College of Cardiff and the University College Hospital Medical School of London, where later he served as physician and investigator. He worked for years as a Beit Memorial Fellow in his animal and clinical investigations and as a member of the Medical Research Council from 1933 to 1937. He was consultant to the City of London Hospital, the Eastern Command, and the Ministry of Pensions, and, at one time (in 1914), when the present writer was working under his direction, he served as medical consultant to the London Zoo, where he was able to secure all kinds of hearts of interest. He gave various notable lectures, including the Oliver-Sharpey, the Linacre, the Harvey and the Herter Lectures in 1914, the Croonian of the Royal Society in 1917, the Royal Medical in 1927, the St. Cyres and Wesley M. Carpenter Lectures in 1931, the Mary Scott Newbold in 1932, the Harveian Oration in 1933, the Huxley Lecture in 1935, and the George Halliburton Hume in 1937. Many honors came to him: C.B.E. in 1920, knighthood in 1921, D.Sc., LL.D., the Royal Medal in 1927, the Copley medal of the Royal Society in 1941, and the Conway Evans Prize in 1944, the last having been presented to him but a few months before his death.

He married Lorna, daughter of Frank Treharne James of Merthyr Tydfil, Wales, in 1916. Their three children are Patricia, Christopher (studying medicine at Oxford), and Philippa, who, because of her tender age, spent four years (1940 to 1944) in this country.

Sir Thomas was always greatly interested in natural history and spent many hours throughout his life studying and photographing birds in their natural surroundings. It had been a hope of his some day to publish his rare collection of bird pictures.

Although it has always been hard to classify Thomas Lewis, his chief contributions were the links he created between physiological knowledge and technique and the medical clinic. Thus he was one of the pioneers in sound clinical investigation, a physiologist in the clinic and a clinician in the laboratory of animal experimentation.

Painstaking, accurate, and indefatigable observation of the processes

TABLE I

CARDIAC ABNORMALITIES OF NINETEEN PATIENTS WITH MYXEDEMA

CASE*	DIAGNOSIS: ETIOLOGICAL†	DIAGNOSIS: ANATOMIC	DIAGNOSIS: PHYSIOLOGIC‡	DIAGNOSIS: FUNCTIONAL§	HEART SIZE ROENTGENOGRAM
1	Arteriosclerosis Hypertension	Coronary sclerosis Hypertrophy and dilatation	First degree A-V block; left bundle branch block; low voltage	Right and left failure—IV	L
3	Hypertension	Hypertrophy and dilatation	Abnormal T waves	Right failure—III	N
4	Arteriosclerosis Hypertension	Hydropericardium Hypertrophy and dilatation Aortic insufficiency		Right and left failure—IV	--
5	Arteriosclerosis	Coronary thrombosis	*Right bundle branch* block; low voltage	Right and left failure—IV	L
6	Arteriosclerosis Hypertension	Coronary sclerosis	Widened QRS complexes; left ventricular strain; low voltage	Left failure—IV	L
8	--------------	Enlargement with mitralization	Prolonged A-V conduction; low voltage	Angina of effort—III	L
9	--------------	Enlargement	Bradycardia; low voltage	Angina of effort—II	L
11	Arteriosclerosis	Hypertrophy and dilatation	Abnormal T waves; low voltage	Left failure—III	L
12	--------------	Enlargement	Bradycardia	Angina of effort—II	L
14	Arteriosclerosis	*Enlargement* Coronary sclerosis	*Multiple auricular extrasystoles*; abnormal T waves; low voltage	Left Failure—IV	L
15	Syphilis Hypertension	Aortitis with aortic insufficiency; hypertrophy left ventricle	Left ventricular strain; low T waves	Angina of effort	L
16	Arteriosclerosis	Coronary thrombosis	--------------------------------	Right and left failure—IV	L
17	Arteriosclerosis	Hypertrophy and dilatation; coronary sclerosis	Intraventricular block; auricular fibrillation; low voltage	Right and left failure—IV	L
19	Thrombosis pulmonary artery	Hypertrophy and dilatation	Prolonged A-V conduction; low S-T segment; low voltage	Right and left failure—IV	L
20	Diabetes mellitus; arteriosclerosis	Hypertrophy and dilatation; coronary thrombosis	Ventricular extrasystoles; low T waves; low voltage	Right and left failure—IV	L
21	Hypertension Arteriosclerosis	Coronary sclerosis	Left ventricular strain	Left failure—III	L
22	--------------	------------------------	Low voltage	Angina of effort—III	L
23	Hypertension Arteriosclerosis	Hydropericardium	Intraventricular block; low voltage	Right and left failure—IV	L
24	Arteriosclerosis	Hypertrophy and dilatation; coronary sclerosis	Low voltage	Right and left failure—IV	L

*Omitted numbers represent cases in the series which showed minimal or insignificant changes. They will be dealt with elsewhere (see reference 12).

†Myxedema is understood to play a causative role in each instance.

‡This includes important electrocardiographic findings.

§Roman numerals refer to the classification of the American Heart Association.

‖L = large.

N = within normal limits.

Original Communications

MANAGEMENT OF THE MYXEDEMATOUS PATIENT WITH SYMPTOMS OF CARDIOVASCULAR DISEASE

THOMAS HODGE McGAVACK, M.D., KURT LANGE, M.D., AND
DAVID SCHWIMMER, M.D.
NEW YORK, N. Y.

THAT cardiac complications are frequent in myxedema is proved by the fact that twenty-four patients with frank myxedema and cardiac complaints have been seen on the wards of a general city hospital within a period of four years. Nineteen (79 per cent) of these were admitted because of the severe cardiac condition, with either right or left ventricular failure, or both. Eight (42 per cent) of these nineteen died. Five died without receiving any thyroid medication, and despite energetic cardiac treatment. Three of these were in the hospital less than forty-eight hours. The other two lived twenty-one and forty-one days, respectively. We believe the status of these patients could have been materially improved by the judicious use of thyroid therapy. On the other hand, it appears that, in two of the three cases in which thyroid hormone was given, its overzealous administration resulted in death.

In ten of the nineteen cases we were able to make serial studies of the basal metabolic rate, the blood cholesterol, the blood proteins, the circulation time, capillary permeability, electrocardiograms, and teleroentgenograms. Out of these observations have come data which may establish useful criteria for following therapy.

METHODS

All patients remained in the hospital for the entire period of study. All laboratory methods were those in common clinical use, with the following exceptions: Cephalin flocculation tests were done by the method originally described by Hanger,[1] using cephalin prepared according to the method of Thudichum;[2] fresh reagent was prepared once weekly, as suggested by others.[3] Drekter's method[4] was used for estimating blood cholesterol; normal levels by this method range from 130 to 200 mg. per 100 c.c., with the free fraction not exceeding 35 per cent of the total. Circulation time and capillary permeability were ascertained

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Read before a scientific session of the New York Heart Association, May 2, 1944.
Aided by a grant from the John and Mary R. Markle Foundation.
Received for publication June 21, 1944.

and whose myxedema was very slight (Case 17, K. B.). Her basal metabolic rate was only −10 per cent. However, her symptoms, signs, and course subsequent to the relief of the cardiac failure fully justified a diagnosis of myxedema, rather than one of simple hypothyroidism. The average blood cholesterol in eighteen cases shortly after admission was 364.3 mg. per 100 cubic centimeters. One of four patients whose cholesterol level was below 200 mg. per 100 c.c. had congenital myxedema, with patency of the ductus arteriosus and other anomalies. He died at the age of 9 months.

TABLE III

DATA FROM INITIAL OBSERVATIONS ON TWENTY-FOUR PATIENTS WITH MYXEDEMA
Blood Cholesterol* (eighteen patients)
Low = 112; High = 750; Average = 364.3

RANGE OF VALUES	NUMBER OF CASES
Below 200	4
Between 201 and 300	5
Between 301 and 400	4
Between 401 and 500	1
Between 501 and 600	2
Above 600	2

*In milligrams per 100 cubic centimeters.

4. Total *blood proteins* and the albumin, globulin, and fibrinogen fractions were ascertained in sixteen cases (Table IV). The highest figure for total protein was 10.52 Gm. per 100 c.c.; the lowest, 6.58; and the average, 8.28. In no instance was the albumin-globulin ratio reversed, but it approached 1 in three cases. Two of these had severe congestive failure at the time the specimens were taken. The third, our oldest patient, aged 71 years (Case 5, S. S.), was severely myxedematous and showed a moderate, anginal type of failure, but no congestive phenomena.

TABLE IV

DATA FROM INITIAL OBSERVATIONS ON TWENTY-FOUR PATIENTS WITH MYXEDEMA
Blood protein* (sixteen patients)
Low = 6.58; High = 10.52; Average = 8.28

RANGE OF VALUES	NUMBER OF CASES
Between 6.5 and 7.5	6
Between 7.6 and 8.0	5
Between 8.1 and 9.0	3
Above 9.0	2

*In percentage.

5. The *circulation time* on, or shortly after, admission, measured by a method previously described by one of us (K. L.[5]), averaged 23.3 seconds in thirteen cases (high normal, 17.5 seconds), with a low of 16 seconds and a high of 31 seconds.

6. *Capillary permeability*, as ascertained by the method of Lange, et al.,[5, 6] was increased in each of the eight cases in which it was studied

by the fluorescein technique of Lange, et al.[5, 6] Any modification of other procedures was chiefly concerned with the methods of taking specimens and the amounts of serum used, as described elsewhere.[7]

INITIAL OBSERVATIONS

The clinical picture of myxedema was present in twenty-four patients, of whom nineteen had cardiac complications.

1. *The cardiac condition* was believed to be due solely to the myxedema in four cases (Table I). Myxedema undoubtedly played a role in every case, but other etiological factors could not be excluded. That is, one patient had syphilitic aortitis; thirteen, arteriosclerotic changes; and five, hypertension with cardiac involvement. Five electrocardiograms revealed changes caused by myxedematous involvement only; nine showed such changes superimposed upon other types of involvement; and, in six, no such alterations could be observed. Myxedema alone produced cardiac enlargement in two instances; in neither of these was pericardial fluid present. The enlargement was associated with hypertension in three cases, and with right and/or left ventricular failure in thirteen cases.

2. *The basal metabolic rate* was measured in nineteen cases (Table II). The lowest rate was –46 (Case 9, R. W.), and the highest, –10 (Case 17, K. B.), with a general average of –25.5 per cent. In seven cases the basal metabolic rate on, or shortly after, admission was obviously elevated as a result of the cardiac condition. Four of these were among the patients with basal metabolic rates between –10 and –19 per cent, and the remainder fell into the group with values between –20 and –29 per cent.

TABLE II

DATA FROM INITIAL OBSERVATIONS ON TWENTY-FOUR PATIENTS WITH MYXEDEMA
(Male, four; female, twenty)
Basal metabolic rate* (nineteen patients)
Low = -46; High = -10; Average = -25.5

RANGE OF VALUES	NUMBER OF CASES
Between -10 and -19	7
Between -20 and -29	8
Between -30 and -39	3
Between -40 and -49	1

Values in percentage.
*Basal Metabolic rate probably influenced by cardiac condition in seven cases, of which four were in the group with rates below -20 per cent.

3. The highest *blood cholesterol* (Table III) was 750 mg. per 100 c.c., which occurred in a 71-year-old patient (Case 5, S. S.) who was admitted to the hospital because of dizziness, attacks of unconsciousness ("fits"), and shortness of breath. Her basal metabolic rate was –22 per cent. The lowest blood cholesterol was 112 mg. per 100 c.c.; this was observed in a 60-year-old woman whose cardiac failure was severe,

ment of the heart was moderate, with the cardiothoracic ratio just above the upper normal limit (0.51) in one (Case 9, R. W.).

SUBSEQUENT DATA AND DISCUSSION

1. In cases of uncomplicated myxedema, a slow, uniformly steady loss of weight was a good index to the effectiveness of therapy, but afforded no help whatsoever when cardiac complications associated with congestive failure existed. Equally unreliable in the latter circumstances were the pulse rate and blood pressure.

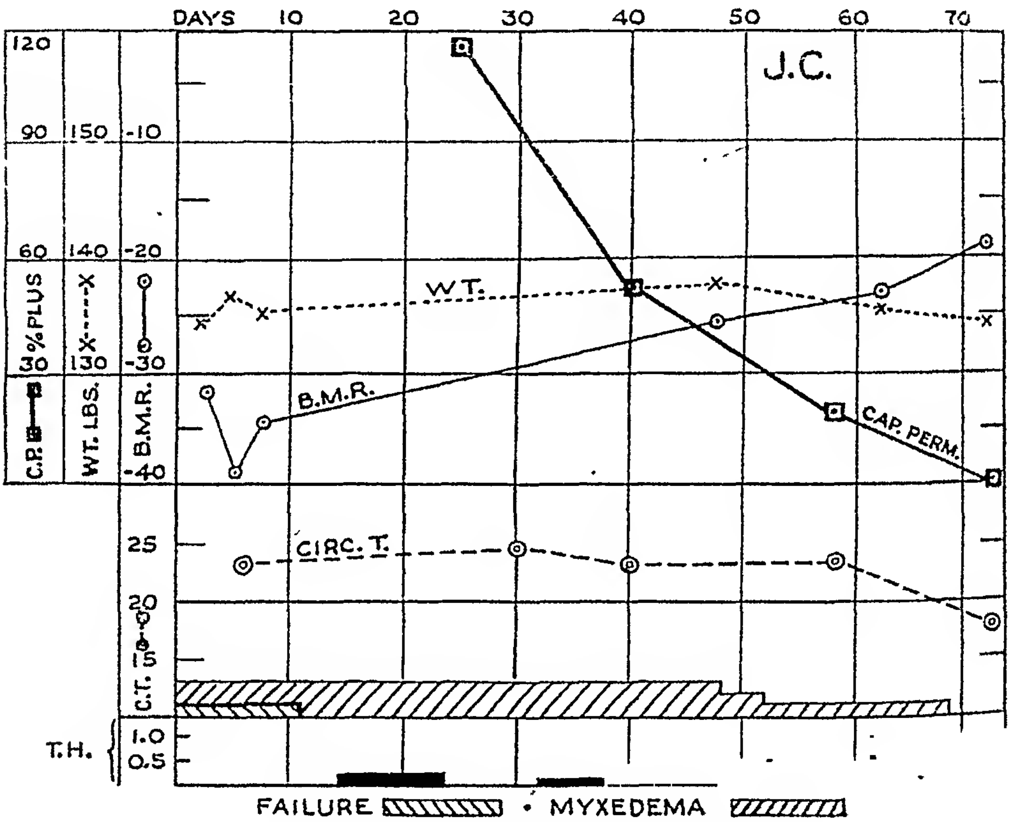


Fig. 2.—Case 8, J. C. Clinical chart. Note the early change in capillary permeability, the gradually rising basal metabolic rate, and the uninformative circulation time.

2. As a result of cardiac failure, the basal metabolic rate was uninformative in at least seven cases at a time when it was important to know whether or not the correct amount of desiccated thyroid substance was being used. The influence of cardiac failure alone is well illustrated in Figs. 2 and 3. In Case 8, J. C. (Fig. 2), the basal metabolic rate decreased from −32 to −39 per cent in three days as a result of improvement in the cardiac status. In Case 16, G. F. (Fig. 3), the rate rose from −24 to −13 per cent in nine days as a result of congestive failure, and fell to −42 per cent as soon as all the cardiac symptoms were controlled and before thyroid medication was begun.

before treatment; the degree of change in one instance reached approximately 165 per cent above the average normal figure, and approximately 130 per cent above the upper normal limit (Fig. 1, tracing of G. F.). Unlike the circulation times and basal metabolic rates, these figures were not appreciably disturbed by cardiac edema, which has been previously shown not to influence capillary permeability.[8]

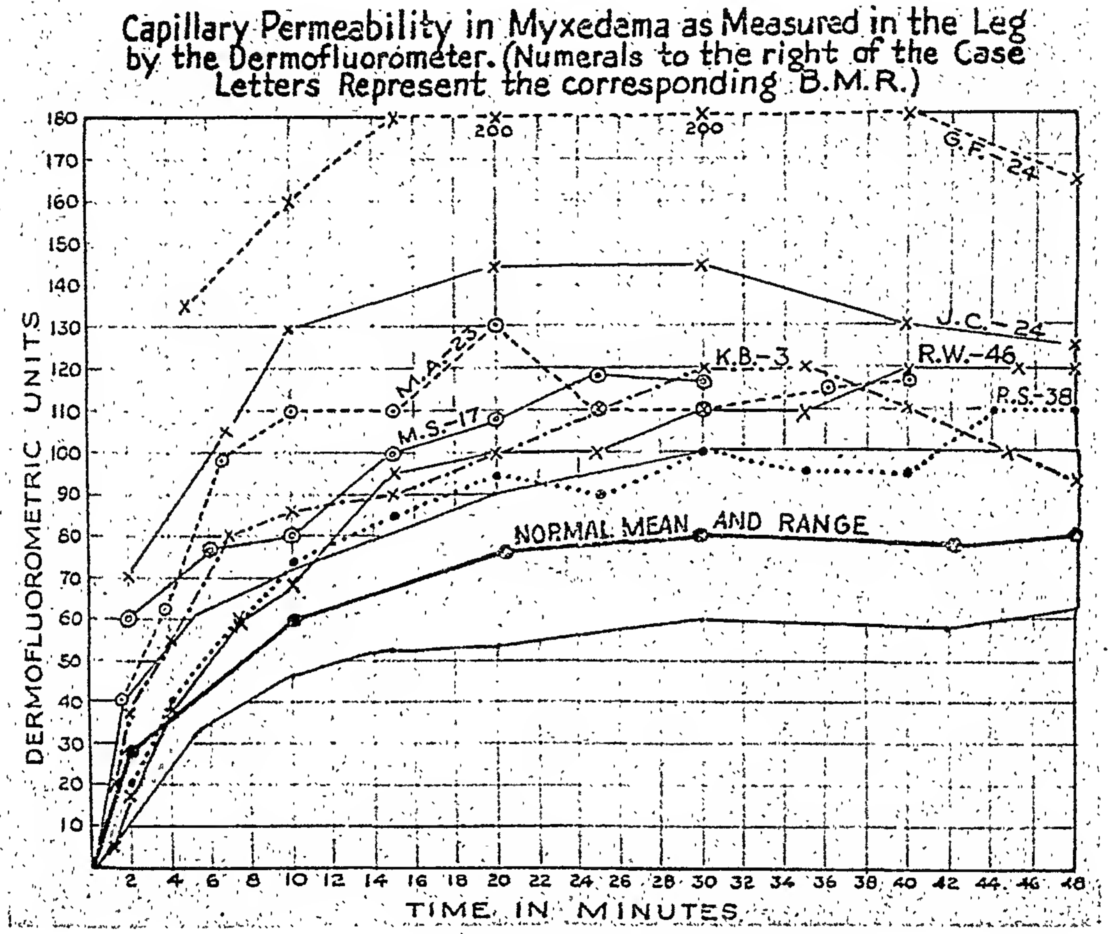


Fig. 1.

7. *Electrocardiograms* were taken on eighteen of the nineteen patients who showed signs of cardiac failure. Thirteen revealed low voltage in all leads and all complexes, and two of these showed no other electrocardiographic evidence of myocardial disturbance.

8. *Roentgenologic examination* of the heart and lungs was carried out on eighteen of the nineteen patients with cardiac failure. In eighteen cases the cardiothoracic ratio exceeded 0.50, and such patients are noted in Table I as having large hearts. Hydropericardium probably accounted for the entire enlargement in one case (Case 23, G. R.), and was diagnosed by physical examination, with subsequent confirmatory tap, in the one case in which roentgenographic study was not performed. In the four cases in which no cause for the cardiac condition other than the myxedematous state could be found, the enlarge-

figures, although the changes might not be sufficiently great to aid in the direction of therapy. In general, the cholesterol levels responded more slowly and more irregularly than did the basal metabolic rate in the patient without heart failure. In the latter state they were a reasonably reliable guide to the patient's thyroid status. For instance, the initial cholesterol level in Case 24 (M. F.) was 340 mg. per 100 c.c. of blood. When her myxedematous state was under satisfactory control, the cholesterol value was never observed to be greater than 200 mg. per 100 cubic centimeters. Conversely, it was never below that figure when any signs of hypothyroidism were present. Moreover, when she was myxedematous without cardiac failure, the levels were approximately the same as when the cardiac symptoms were in evidence. In

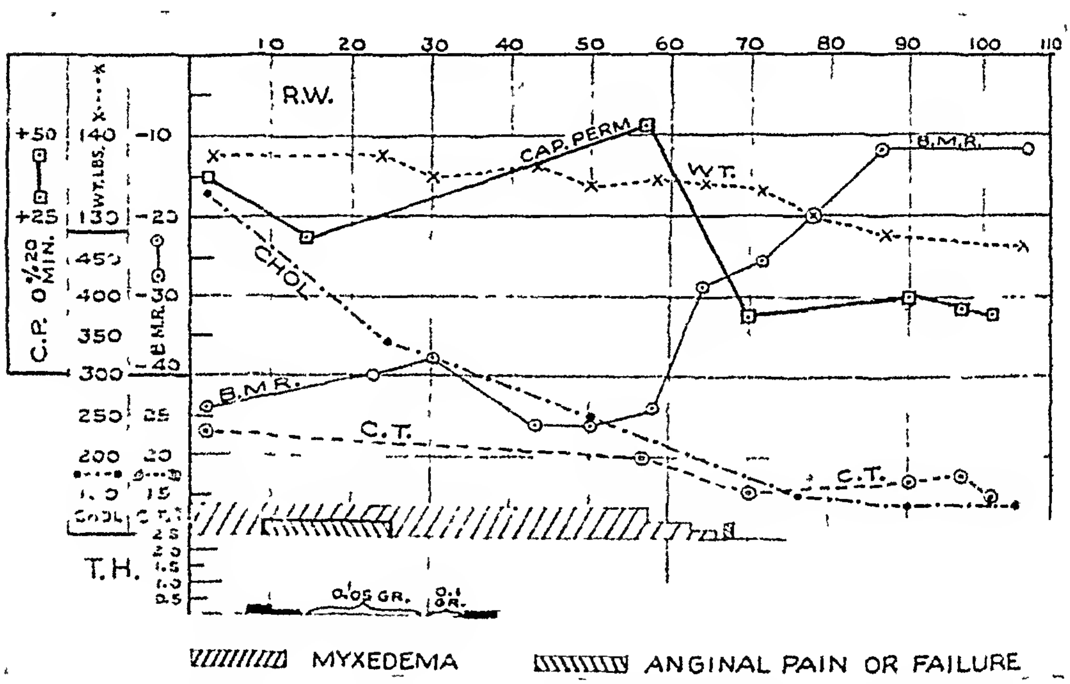


Fig. 4.—Case 9, R. W. Clinical chart. This record shows the response in a case of myxedema in which severe signs of failure never occurred.

other words, the total value seemed to be independent of her cardiac status, although the percentage of esters might be adversely influenced thereby. The change in cholesterol toward normal is of much more significance than the absolute level itself. This is illustrated in Case 16 (Fig. 3), in which the cholesterol level fell 260 mg. per 100 c.c. of blood between the twenty-sixth and seventieth days of observation, with simultaneous, favorable changes in basal metabolic rate and capillary permeability. The resulting level was still high (380 mg. per 100 c.c.), and the patient still had severe hypothyroidism, but was definitely improved. In Case 9 (R. W.) the changes were equally dramatic; normal levels were not reached until capillary permeability was normal and the basal metabolism had markedly improved (Fig. 4).

Changes in the basal metabolic rate in cardiac disease have not been satisfactorily explained. At least two factors may alter the basal metabolic rate in cardiac failure. Dyspnea increases muscular effort and, therefore, the oxygen consumption. Edema increases weight and, therefore, lowers the calculated basal metabolic rate. However, the influence of the first of these two opposing mechanisms usually outweighs the second, so that the net result is usually a more or less marked elevation of the metabolic rate.

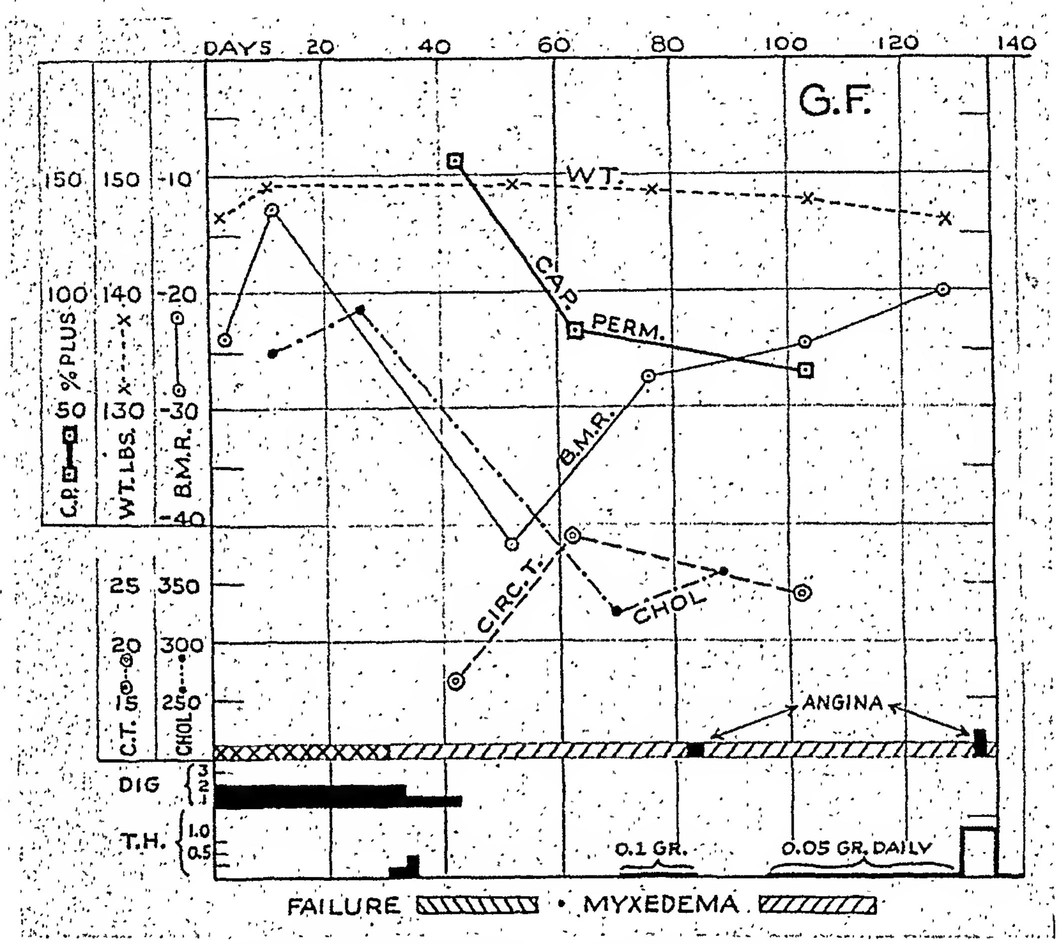


Fig. 3.—Case 16, G. F. Clinical chart. Note the false basal metabolic rate as a result of cardiac failure, with true figure about the fortieth day of observation. Capillary permeability was altered toward normal, along with cholesterol and the basal metabolic rate.

3. Values for total cholesterol were highly informative in confirming the presence of myxedema; normal levels were found in only four of twenty-four cases. Except in longstanding right-sided heart failure, the ratio of cholesterol in the free and combined forms was invariably within normal limits, whether the patient was in a myxedematous state, in cardiac failure, or normally controlled. When levels were originally high while myxedema existed, subsequent variations were always influenced by the degree of thyroid sufficiency; the value decreased with every increase in the basal metabolic rate, and in all instances attained normal levels when the patient's thyroid status was fully restored to normal. Similar variations occurred in patients with initially normal

4. If the figures for total blood proteins were above normal, they were of confirmatory value in establishing the diagnosis of myxedema. However, 36 per cent were well within normal range, and an additional 31 per cent could be looked upon as high normals (Table IV). Neither the total figure nor any fraction thereof was of any value in following the progress of the patient. The albumin-globulin ratio was equally uninformative. Under treatment with thyroid substance, high values were brought within the normal range, but the degree of change never reflected the patient's general condition, nor did it indicate thyroid status at any particular moment. In the interests of simplicity, serial figures for proteins have, therefore, been omitted from all of the graphs.

5. In the presence of both myxedema and cardiac failure, the circulation time is a totally unreliable method of gauging the progress or course of either. Of the two conditions, congestive failure has a more profound effect in raising the circulation time than does myxedema. The most marked increases were noted when both were present simultaneously. Case 8 (Fig. 2) illustrates the difficulty encountered in evaluating this test. The circulation time remained at a constantly high level until convalescence was well established.

6. Capillary permeability cannot be quantitatively measured in the Negro race, but in the white patient it has afforded one of the earliest and most reliable signs of diminution of the myxedema. It has been followed for periods of two to ten months in five cases. The records of some of these are shown graphically in Figs. 2 to 5, inclusive. The profound increase observed in myxedema shows improvement before it has been indicated by any other objective measure we have used. This test has the distinct advantage of being uninfluenced by cardiac decompensation.[8] The fluctuations in permeability are, moreover, quantitatively large (Figs. 2, 4, and 5), so that relatively slight improvement in the general condition of the patient is reflected in the curves obtained.

7. Electrocardiograms that showed changes due only to the myxedematous state were present in three of the nineteen patients who entered the hospital primarily because of the cardiac disturbance. In these, serial examinations showed a return to normal as the myxedema was relieved. In the serial tracings of R. W. (Case 8, Fig. 6), the bradycardia and the low voltage originally present in all complexes of all leads gave way gradually to a normal electrocardiogram as the myxedematous state disappeared under steadily increasing doses of thyroid hormone. The relationship of these cardiac changes to the other clinical data is readily appreciated by referring to Fig. 4, the "first day" of which is April 7, 1943. On the seventieth day of observation, June 16, 1943, the basal metabolic rate was rising, but was still far from normal (−26 per cent); the circulation time was for the first time within normal limits (16 seconds); the capillary permeability was normal; and the blood cholesterol several days later was 150 mg. per

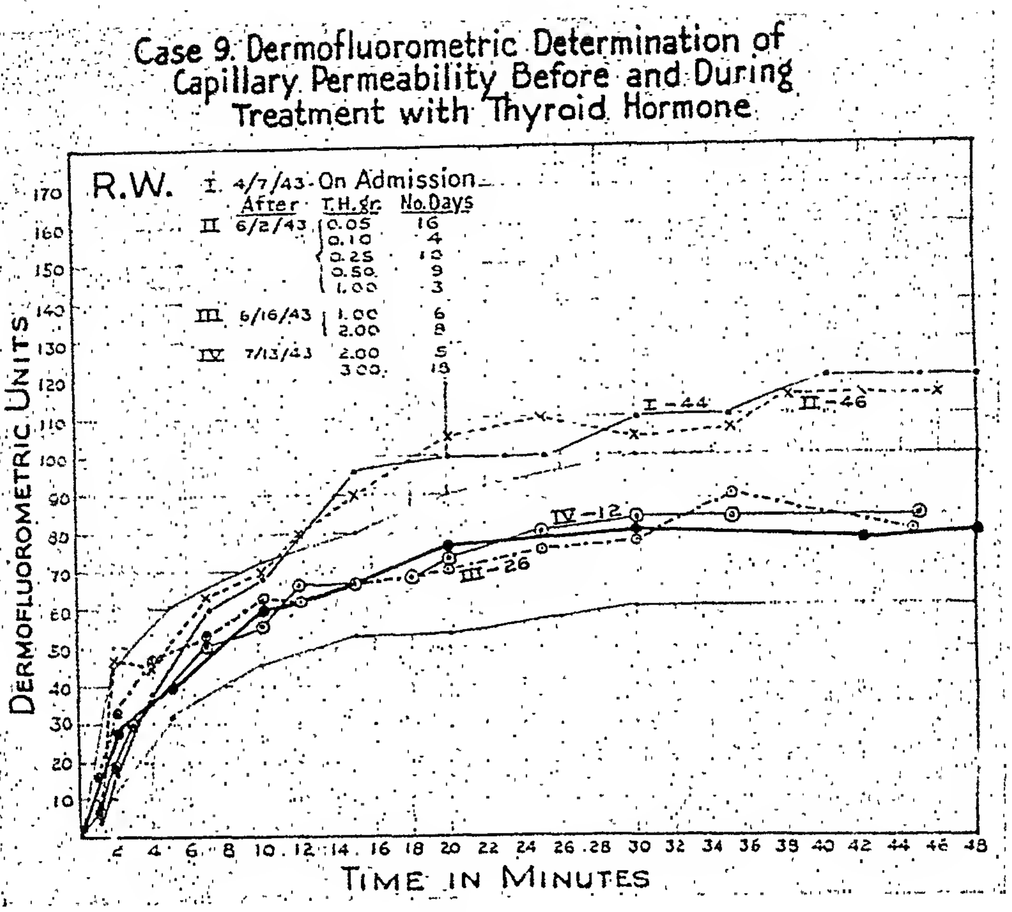


Fig. 5.

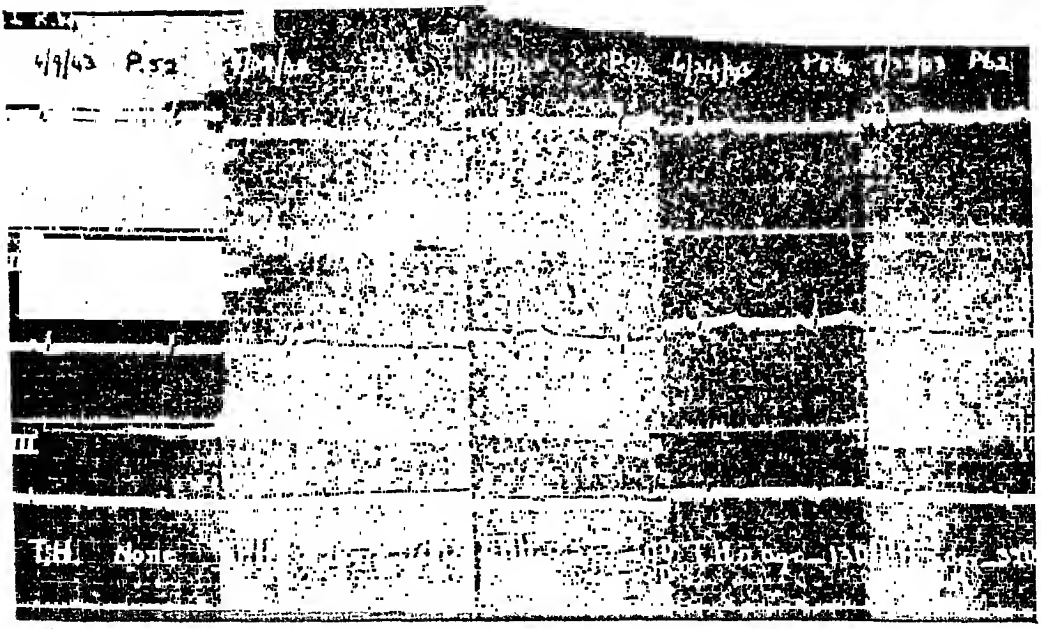
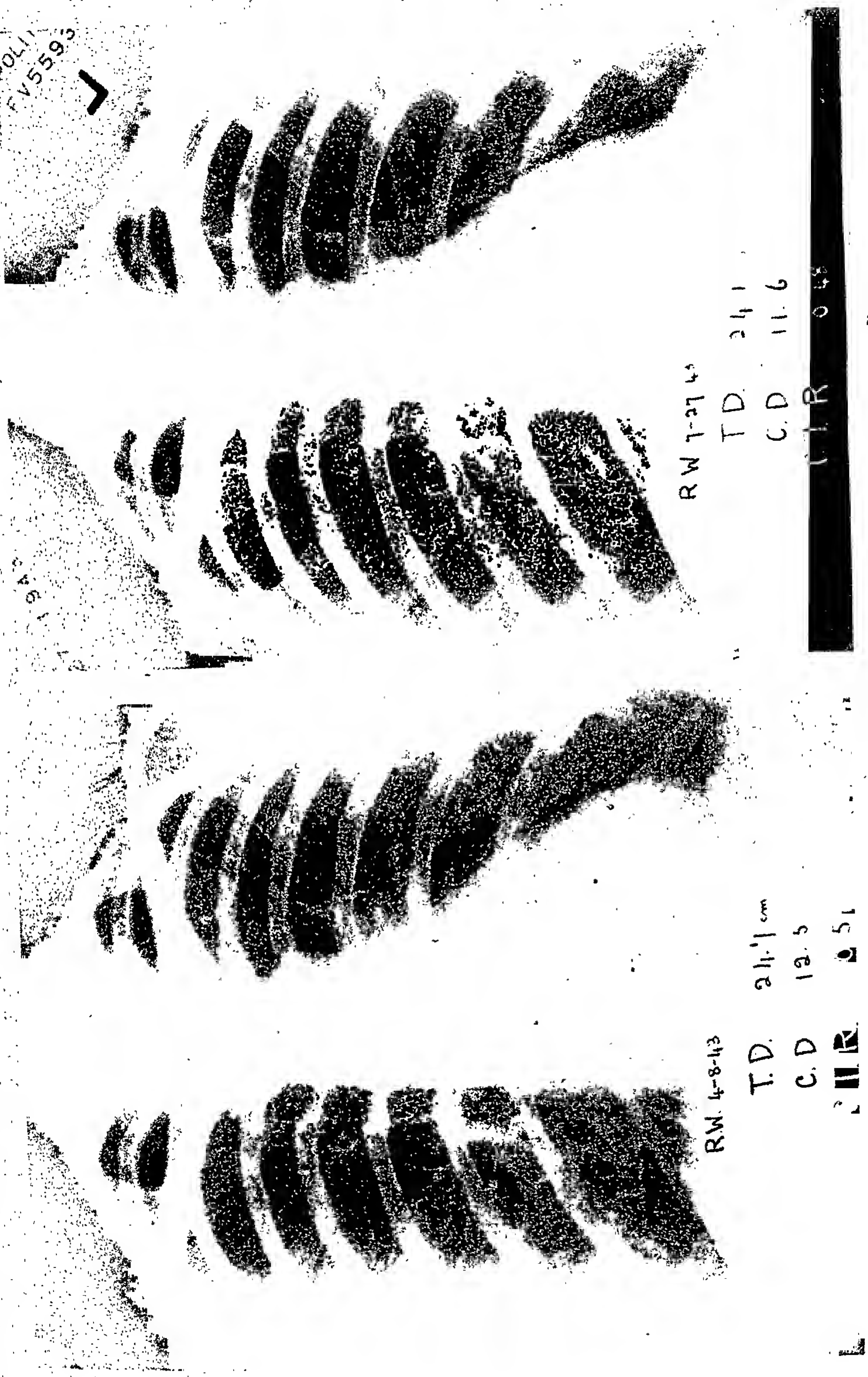


Fig. 6.—Electrocardiograms in Case 9, R. W. April 9, 1943, bradycardia and low voltage in all complexes. May 27, 1943, after a total of 5.5 grains desiccated thyroid substance taken in sixteen days without appreciable change. June 10, 1943, eighteen days later, during which 13.5 grains thyroid hormone were taken. Note increased amplitude of all complexes; T_2 still very low. Capillary permeability still high. June 24, 1943, T_2 greater than 1 mm.; capillary permeability normal. Basal metabolic rate still low, –26 per cent. July 23, 1943, patient clinically well; basal metabolic rate, –12; and capillary permeability normal.

100 cubic centimeters. Complete disappearance of the abnormal electrocardiographic features occurred between June 10, 1943, and June 24, 1943. That capillary permeability simultaneously decreased to slightly below the average normal mean, despite the continuation of a slow pulse rate and a low basal metabolic rate, would appear to be more than coincidental. It leads us to believe that changes in the capillary permeability of the cardiac musculature may have something to do with the low voltage which is usually present in cases of uncomplicated myxedema. Just what disturbances of water and electrolytic balance accompany this altered capillary state it is at present difficult to say. In any event, they seem to be capable of materially decreasing the functional capacity of the heart in such a manner as to lower its tolerance for thyroid hormone. Gradual improvement in the electrocardiogram and normalization of the capillary permeability curves appear to be satisfactory and safe guides for the administration of thyroid hormone to the myxedematous patient with cardiac failure, for their change toward the normal apparently goes hand in hand with a restoration of electrolytic, water, and nutritional balance within the tissues themselves.

8. Cardiac enlargement in the patient with myxedema uncomplicated by congestive failure or hypertension was rarely observed in the group of cases here studied. However, serial examinations in Case 9, R. W., afforded a comparison of the size of the cardiac silhouette before and after treatment. This patient had myxedema of severe degree and long standing which was complicated only by mild angina of effort. The size of the heart, therefore, would be expected to reflect only changes secondary to the myxedematous state. On admission, slight enlargement was noted (Fig. 7, *A*), with a cardiothoracic ratio of 0.51. Just prior to discharge, one hundred seven days later, after adequate thyroid therapy, the cardiothoracic ratio was 0.48, with a frontal cardiac area of normal proportions (Fig. 7, *B*). The improvement appeared concomitantly with stabilization of the patient's condition clinically and a return to normal of the other laboratory data. There is much dispute as to the nature of the cardiac enlargement in uncomplicated myxedema, but LaDue[9] has critically analyzed the problem in connection with a pathologic study of a patient who died with a "myxedema heart." Histologically, the lesions were not distinguishable from those of several other conditions, but, therapeutically, changes in cardiac function in myxedema responded quite specifically to thyroid hormone. The slight enlargement detectable roentgenographically would appear to be due to the interstitial edema that has now been described by several investigators.[9-11, 13] This concept receives support from the simultaneous disappearance of the abnormal changes in capillary permeability, the electrocardiogram, and the cardiac silhouette of the patient whose data we have just presented.

9. Therapy. The ill effects of initially high doses of thyroid (i.e., more than 0.5 grain daily) are illustrated nicely in Cases 1, 8, 9, 11, 12,



A. B.

Fig. 7.—Case 9, R. W. Roentgenograms of the heart at 2 m., *A*, before treatment, and *B*, after treatment. Relatively uncomplicated myxedema enlarges the heart, an effect which thyroid hormone specifically abolishes.

of cardiac symptoms, and in four cases a smaller amount was used initially because of the patient's unsatisfactory cardiac status. In the cases in which treatment was finally adequate, the dosages necessary to keep the patients free of the symptoms of thyroid insufficiency varied from 0.5 to 3 grains daily.

CASE HISTORIES

Case histories for the majority of our patients will be summarized elsewhere.[12] Below appear the detailed records of the three patients whose conditions have been utilized extensively for illustrative purposes in the correlation of data and illumination of discussion. Case numbers here and in Table I are in chronological relation to the series as a whole.

CASE 8.—J. C., a 49-year-old white woman, was admitted to the hospital because of nocturnal "fits," exertional dyspnea, and precordial pain, the first two of several months' duration, and the last mentioned occurring for several days in conjunction with the dyspnea. The fits were described as left-sided "shaking spells," each lasting fifteen to ninety minutes without loss of consciousness, associated with vertigo, blurring of vision, spots before the eyes, and chattering of the teeth. For "more than a year," the patient stated she had been unusually sluggish and had "felt heavy, big, and awkward." For many years she had felt weak, had been pale, and tired easily.

Her father died at the age of 59 years of diabetes. She was one of seven siblings; two sisters "had heart trouble." There was no family history of any thyroid disturbance or of unusual skeletal development. She had had uncomplicated scarlet fever at the age of 11 years, mastoiditis which necessitated operation at the age of 37 years, and pneumonia at the age of 47 years. There had been vague "growing pains" in early life, but the patient had no knowledge of rheumatic fever or its complications. Her menses had begun at the age of 13 years, and had recurred irregularly until the age of 15 years; each period lasted three or four days, with scanty flow. There was complete cessation until the age of 21 years, when, after marriage, the menstrual flow returned at fairly regular intervals until the age of 25 years. Complete amenorrhea followed the birth of her second child at that age.

Physical examination revealed a stockily built, well-nourished, mentally and physically sluggish woman whose height was 59 inches; the lower measurement was 29 inches, and her weight was 134 pounds. Her skin was pale, thickened, coarse, and dry. The supra-orbital, axillary, and pubic hair was scanty, and that of the scalp, coarse and dry. The facies was mongoloid, with thick, heavy lips, slitlike orbital fissures, puffiness of the eyelids, and loss of expression. The tongue was large and thick, and the mouth was open a great deal of the time. The thyroid was readily palpable; the left lobe was somewhat uniformly enlarged, but of normal consistency. The lungs showed evidence of basal congestion. The heart was enlarged, with straightening of the left border. There was a rumbling presystolic and systolic apical murmur, with accentuation of the pulmonic second sound. The ventricular rate was 72; the blood pressure, 112/80. Her knee jerks were sluggish. No pathologic reflexes were elicited. The laboratory data on, or shortly after, admission included a negative urinalysis, negative blood Wassermann and Kahn reactions, and a basal metabolic rate of −39 per cent. The hemoglobin was 89 per cent, the erythrocyte count, 4,080,000 per

16, 22, and 24. In two instances (Cases 8 and 9) the dose had to be adjusted at levels as low as 0.05 grain daily before cardiac distress could be avoided.

In every case, from the standpoint of treatment, the cardiac disturbance was given precedence over the hypothyroidism, but the patient's condition was never fully satisfactory until both were treated. The unfavorable influence of the hypothyroid state upon cardiac function is well illustrated in Case 24 (M. F.). This patient, on the three hundred sixty-seventh day of observation, was taken off her previously satisfactory regime of 3 grains of digitalis daily and 1 grain of desiccated thyroid substance daily. Signs of myxedema were marked about sixty days later, but no evidence of cardiac failure appeared until two weeks after the myxedematous state had been established. It would appear from this and other observations that we cannot improve the cardiac status by completely withholding all thyroid therapy. As a matter of fact, it is our opinion that the heart condition grows steadily worse, despite routine measures, when this is done. Patient 16, G. F. (Fig. 3), affords another good example of this. Her mild right- and left-sided cardiac failure was completely relieved by rest in bed and digitalis therapy, but the added cardiac load produced by the administration of as little as 0.1 grain of thyroid was sufficient to cause severe anginal distress. Later, these signs failed to make their appearance with 0.05 grain of desiccated thyroid substance daily. Between the ninety-sixth and one hundred thirtieth days of treatment (Fig. 3), there was gradual improvement in the patient's status, as reflected in increasing activity without cardiac signs, decreasing capillary permeability, and a slowly rising basal metabolic rate. There is reason to believe that the sudden increase in demands upon the heart which followed a sharp increase in the dose of thyroid to 1 grain daily was a precipitating factor in her death from coronary occlusion.

The experiences mentioned serve to emphasize the fact that the doses of thyroid must be small at first and *very gradually* augmented. The actual amount initially selected, the rate of increase, and the stabilization figure will depend upon many factors, but the age of the patient, the known duration of the disease, and the degree of demonstrable impairment of cardiac function are of primary importance. In view of the careful clinical and pathologic studies that have been made of the "myxedema heart,"[9, 13] these points should need no emphasis. Yet, clinically, in our experience they are neglected features of therapy. The death of two patients (Cases 1 and 16) followed comparatively large initial doses of thyroid, or a too sudden, relatively large increase in the amount administered. Other patients showed severe aggravation of symptoms when similarly treated.

As a rule, a daily dose of 0.25 grain of desiccated thyroid substance was tolerated at the beginning of treatment. However, in two cases this amount had to be reduced considerably because of the aggravation

verity. These symptoms began after an operation for "ruptured appendix, ureteral stone, and dropped right kidney." Hoarseness, dryness of the skin without tendency to perspire even in the summertime, and constipation had been present for several years. Palpitation, substernal oppression, dyspnea, and swelling of the hands and face, in association with a gain of 10 pounds in weight, had been noticed by the patient and her family for four to five months. The patient had been variously treated through twelve years for psychoneurosis, anemia, "kidney disease" and "female trouble."

Most of her earlier history was irrelevant. Her menses began at the age of 12½ years, and had recurred regularly at twenty-eight-day intervals, with a scanty flow lasting three days. Although she had been married for twelve years, she had never experienced normal libido or orgasm, and there had been no children although contraceptives had never been used.

Her father died at the age of 72 years of carcinoma of the stomach. Her mother died at the age of 54 years of "heart trouble." One brother, aged 42 years, had rheumatic heart disease. One sister, now aged 38 years, has been operated on "for a goiter."

Physical examination revealed a pale, cooperative, intelligent, but slowly responding woman, 64½ inches tall and weighing 137 pounds. Her skin and hair were dry, thickened, and coarse. The face was puffy and swollen, particularly about the eyes. Slight exophthalmos was present. Thyroid tissue could be palpated over the thyroid cartilage, but was decreased in amount. The lungs were normal. The heart was not enlarged. The apex beat was not visible or easily palpable. The heart sounds were distant; no thrills or murmurs were present. The ventricular rate was 54, and the blood pressure, 98/78. The extremities were cold, dry, and myxedematous.

Laboratory data on, or shortly after, admission included a negative urinalysis, negative blood Wassermann and Kahn reactions, a negative cephalin flocculation, a negative direct van den Bergh, and a basal metabolic rate of –46 per cent. The icteric index was 6.5 units, and the blood phosphatase, 2.2 Bodansky units. Her blood sugar in milligrams per 100 c.c., fasting, and at half an hour, one and a half, two and a half, and three and a half hours after the ingestion of 100 Gm. of glucose, was 90, 155, 180, 110, and 70, respectively. The total blood proteins were 7.87 per cent; the albumin fraction was 5.35 per cent, the globulin fraction, 2.50 per cent, and the albumin-globulin ratio, 2.12. Other blood chemical values in milligrams per 100 c.c. were: urea nitrogen, 12.1; creatinine, 1.1; phosphorus, 3.5; total cholesterol, 544; free cholesterol, 200 (37 per cent). Her hemoglobin was 69 per cent. There were 3,630,000 erythrocytes and 6,350 leucocytes per cubic millimeter of blood. The percentual partition of leucocytes was: polymorphonuclear forms, 25; lymphocytes, 69; transitional forms, 3; eosinophiles, 2; and basophiles, 1. Her circulation time was 24 seconds (fluorescein method). Her capillary permeability at twenty minutes was 38 per cent above normal. Her electrocardiogram (Fig. 6) showed sinus bradycardia (rate 60), with very low voltage of all complexes. T waves were absent from Lead I and inverted in Leads II and III. Roentgenograms of the skull, chest, wrists, gastrointestinal tract, and biliary passages revealed no organic disease. The heart was slightly enlarged, with a cardiothoracic ratio of 0.51.

Diagnosis.—Myxedema, with myxedema heart.

cubic millimeter, and the leucocyte count 6,500 per cubic millimeter, with a percentual differential count of polymorphonuclear cells, 60; lymphocytes, 34; transitional forms, 2; and eosinophiles, 4. On two occasions free hydrochloric acid was absent from the stomach contents after the administration of histamine; the total acid was low, never rising above about 10 units. Fasting and hourly blood sugar levels in milligrams per 100 c.c., after the oral administration of 100 Gm. of glucose, were 95, 130, 143, 145, 93, and 95, respectively. The speed of sedimentation of her erythrocytes (Westergren method) was 4 mm. in fifteen minutes, and 39 mm. in an hour. In percentage, her total serum proteins were 7.38; the albumin was 4.74, and the globulin, 2.64, with an albumin-globulin ratio of 1.78. Her icteric index was 6.5; the cephalin flocculation test was negative; the van den Bergh reaction was of the direct negative type; and blood phosphatase was 3 Bodansky units per 100 cubic centimeters. Other blood chemical values in milligrams per 100 c.c. were: calcium, 10; phosphorus, 3.3; total cholesterol, 260; free cholesterol, 76 (34 per cent); chlorides (as sodium chloride), 545; urea nitrogen, 14; and creatinine, 1.2. Roentgenograms of the skull and wrist failed to show any bony abnormalities. Roentgenologic examination of the alimentary tract revealed no evidence of disease. There was enlargement of the cardiac shadow, with straightening of the left border (mitralization). The electrocardiogram showed normal sinus rhythm, with an average rate of 64 per minute. The P-R interval was prolonged to 0.24 second. There was low voltage of all complexes in each of the leads, with an R_2 of 5 mm., no T wave greater than 0.5 mm., and inversion of T_3. The circulation time was 23 seconds (fluorescein method). The capillary permeability was 51 per cent above normal at the ten-minute interval.

Diagnosis.—Myxedema with "myxedema heart"; old, inactive rheumatic heart disease with mitral valvulitis; generalized arteriosclerosis, most marked in the cerebral vessels; and tonic left-sided convulsions resulting from the combined effects of myxedema and cerebral sclerosis.

Her *course* in the hospital is graphically depicted in Fig. 2. Her pulmonary congestion and anginal pain quickly subsided with rest in bed. She was then given desiccated thyroid substance in a dose of ¼ grain daily for nine days, whereupon the angina pectoris returned. After a rest period of nine days, during which cardiac symptoms again disappeared, thyroid medication was resumed with a dose of ⅛ grain daily. This was gradually increased until, at the time of discharge, seventy-four days after admission, she was taking 1 grain daily without untoward reaction. Her circulation time, blood cholesterol, and capillary permeability were normal. Her basal metabolic rate was still low (−19 per cent), and her electrocardiogram was improved, with the appearance of positive T waves and an increase in the height of the QRS complexes. From Fig. 2 it will be noted that a decrease in capillary permeability went hand in hand with an increase in the basal metabolic rate; the former change was greater and more dramatic than the latter. The circulation time returned to normal much more slowly. The patient was finally stabilized on 1½ grain of desiccated thyroid substance daily, with complete disappearance of generalized and cardiac signs of myxedema.

CASE 9.—R. W., a 35-year-old, white married woman, was admitted to the hospital because of excessive nervousness, irritability, apprehensiveness, "inability to accomplish things," coldness, and belching after meals, all of thirteen years' duration and of gradually increasing se-

Other blood chemical values in milligrams per 100 c.c. were: urea nitrogen, 11; creatinine, 1; phosphorus, 2.3; total cholesterol, 480; and free cholesterol, 120 (25 per cent). The hemoglobin was 82 per cent; there were 3,140,000 erythrocytes and 12,200 leucocytes per cubic millimeter of blood. The electrocardiogram showed rather marked left axis deviation and evidence of posterior wall infarction. Teleroentgenograms of the chest revealed slight enlargement of the heart. Later, after the cardiac condition was well compensated, but before thyroid therapy was begun, the circulation time was 16 seconds, and the capillary permeability at the end of ten minutes, about 151 per cent of normal.

Diagnosis.—Myxedema; coronary sclerosis with coronary occlusion; generalized arteriosclerosis, probably with preexisting hypertension.

Under digitalis, this patient's cardiac failure disappeared rapidly, her pain ceased, and the basal metabolic rate dropped to −42 per cent. On the seventieth day of hospitalization, the administration of thyroid was begun with a dose of 1/10 grain of the desiccated material daily. On the fourteenth day after it was begun, the patient complained of severe anginal pains; these ceased within two days after the drug was stopped. Seven days later, 0.05 grain daily was administered without ill effect, although the patient was allowed to be up and about the ward. Thirty-three days later, 1 grain of thyroid was administered daily. On the morning of the fifth day thereafter, the patient developed severe precordial pain and went rapidly into shock. An electrocardiogram, taken the next day, showed evidence of a fresh coronary occlusion. The patient died one day later. It is interesting and important that, although 0.05 grain of thyroid improved the extremely low basal metabolic rate and reduced the capillary permeability, it had no constant influence upon the circulation time or marked effect upon the blood cholesterol.

SUMMARY

1. In myxedema, variations in blood proteins are of no value in following the results of therapy.

2. In myxedema with cardiac failure, variations in the weight of the patient, his basal metabolic rate, and his circulation time are of no value in ascertaining his thyroid status at any particular moment.

3. When taken in conjunction with the initial level, i.e., before treatment, the total blood cholesterol has been a very reliable method of ascertaining the degree of thyroid sufficiency in myxedema with cardiac failure, for it is uninfluenced by the latter in the absence of signs of liver damage.

4. An increase in capillary permeability is a constant feature of myxedema. A decrease from the initially high permeability is one of the earliest and most constant signs of improvement.

5. Thyroid therapy must be used cautiously in myxedema with cardiac failure. The dose should be sufficiently small to avoid an aggravation of the cardiac phenomena, but, no matter how severe the failure is, some hormone should be used. An effort should be made to make the initial dose sufficiently large to effect a decrease in capillary permeability.

The *course* of this patient in the hospital is shown graphically in Fig. 4. In addition to the data there charted, her blood proteins were followed serially, and there was a decrease to low normal levels as soon as thyroid therapy became effective. Free and ester fractions of cholesterol are not given in the graph because they were always percentually normal. One-fourth grain of desiccated thyroid substance, begun on the seventh day after admission, produced a rather severe exacerbation of her anginal pain, and not until it was reduced to $\frac{1}{20}$ grain did this disappear. Later the dosage was slowly increased at approximately ten-day intervals, so that, successively, 0.1, 0.25, 0.50. 1, 2, and 3 grains were taken. As judged by the clinical observations, the capillary permeability changes, the blood cholesterol levels, the circulation times, and the electrocardiograms, the patient's myxedema disappeared on or about the fiftieth day after treatment was begun, and after she had received 2 grains of thyroid for five or six days. However, the basal metabolic rate was still extremely low (–29 per cent), and the disease was not deemed to be controlled fully until 3 grains of thyroid had been used for approximately two weeks, at the end of which time the basal metabolic rate was –12 per cent. It was not until this level of dosage was reached that she lost all of her gastrointestinal symptoms and her vague aches and pains. Since her discharge from the hospital, her maintenance dose has remained at 3 grains daily.

CASE 16.—G. F., a 63-year-old, white widow, was admitted to the hospital on the day of an attack later proved to be one of coronary occlusion. She had suffered intermittently from precordial pain for about two years, and had had a severe attack two months prior to admission, which had not, however, confined her to bed. For two years she had noticed sensitiveness to cold, constipation, increasing hoarseness, dryness of the skin and hair, with absence of sweating, and a slow, steady gain in weight. Her past and family histories were noncontributory. Her menses had begun at the age of 13 years, had occurred "monthly," lasting four to five days, and had not been associated with clots, pains, or other distressing symptoms. She had been pregnant three times and had three children. Her menopause appeared spontaneously and apparently asymptomatically at the age of 30 years.

The patient was a moderately obese, rather apathetic person, complaining of precordial pain. Her weight was 146½ pounds; her height, 60½ inches; her temperature, 99° F.; her pulse rate, 100; and her respirations, 28. Her skin was cold, dry, thickened, and tough. The hair was moderately coarse. The heart was enlarged to the left and downward; the heart sounds were faint; and there were no thrills or murmurs. The blood pressure was 140/60, and remained near that level until her death, on the one hundred twenty-seventh day after admission. A few moist râles could be heard at the bases of both lungs. The edge of the liver was palpated two fingerbreadths below the costal margin. There was generalized myxedema, but no evidence of pitting edema in any part of the body.

On, or shortly after, admission, her urinalysis was negative; her blood Wassermann and Kahn reactions, negative; her van den Bergh, direct, negative; her icteric index, 5; her blood phosphatase, 7.7 Bodansky units; her cephalin flocculation, negative; and her basal metabolic rate, –24 per cent. The speed of sedimentation of her erythrocytes was 60 mm. in fifteen minutes and 130 mm. in an hour (Westergren method). The blood albumin, globulin, and total proteins were 4.73, 3.17, and 7.90 per cent, respectively, with an albumin-globulin ratio of 1.48.

ELECTROCARDIOGRAPHIC STUDY OF DEFORMITY OF THE CHEST

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CARDIAC signs and symptoms produced by chest deformity have been described largely by continental European writers. In 1878, hypertrophy of the right ventricle in a case of high-grade scoliosis was noted by Traube.[1] Since then a large number of articles have appeared in the French,[2-5, 25] Italian,[6] and German literature.[7-9] The best piece of work among them was done in 1899 by Bachmann, who reported 197 autopsy cases of scoliosis, most of which showed right ventricular hypertrophy and dilatation. In later years the role that this factor can play in determining cardiac failure has become more prominent in the English literature.[10-22]

In spite of all these investigations we have only very scattered data from the electrocardiographic standpoint. The majority of investigators agree that a high percentage of patients with chest deformity show hypertrophy and dilatation of the right-sided cavities in so far as the pathologic examination is concerned, but relatively few electrocardiograms have been mentioned. These have shown right axis deviation or a tendency toward it.[18, 20] Edeiken[13] took electrocardiograms of eighteen otherwise unselected patients with deformed chests and reported that "except for axis deviation the tracings were normal in 16 instances."

PRESENT STUDY

In order to obtain more adequate information than now exists concerning the effect of chest deformity, as such, on the electrocardiogram, we have studied one hundred deformed patients. We have purposely avoided patients with obvious cardiac damage, myocardial, valvular, or pericardial. Moreover, we have selected patients without pulmonary disease which might add an extra strain on the right side of the heart, in addition to that due to the deformity of the chest itself. Under these conditions we believe that the electrocardiographic abnormalities which we have found have not been influenced by heart or lung disease per se.

We selected cases of young persons, mostly between 15 and 25 years of age, with normal blood pressure and without râles at the bases of the lungs, constant heart murmurs, gallop rhythm, engorged jugular veins, increased liver volume, or pitting edema. We found that some symptoms, such as slight or mild dyspnea on effort, are not reliable clues of myocardial reserve because of the great diminution of the vital capacity in most of our cases.

Also, we carried out roentgenologic studies of the heart and lungs, looking for any definite partial or total enlargement of the heart and

Received for publication June 23, 1941.

6. Satisfactory initial daily doses of thyroid hormone, as desiccated thyroid substance, have ranged from 0.05 to 1 grain. In thirteen cases, stabilization was attained through the daily use of amounts varying from 0.5 to 3 grains.

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TABLE I

NUMBER	AGE (YR.)	TYPE OF DEFORMITY	VITAL CAPACITY (PER CENT OF NORMAL)	AXIS SITTING DEGREES	AXIS RECUMBENT DEGREES
1. R. V.	14	Right dorsal, left lumbar	42	45	52
2. M. M.	24	Right dorsal. left lumbar	20	90	80
3. H. A.	13	Right dorsal, left lumbar	16	110	105
4. P. V.	12	Total left	41	52	30
5. E. W.	22	Right dorsal, left lumbar	39	56	48
6. D. R.	25	Right dorsal, left lumbar	112	33	33
7. G. T.	15	Right dorsal, left lumbar	38	32	30
8. J. McC.	14	Right dorsal, left lumbar	81	92	80
9. C. B. C.	13	Right dorsal, left lumbar	68	87	80
10. R. B.	24	Right dorsal, left lumbar	42	20	23
11. W. D.	19	Kyphosis	68	43	55
12. L. F.	15	Left total	52	85	85
13. B. E.	15	Right dorsal, left lumbar	35	90	90
14. E. S.	13	Right dorsal, left lumbar	92	85	70
15. A. M.	26	Right dorsal, left lumbar	32	20	25
16. M. F.	19	Right dorsal, left lumbar	66	90	85
17. J. S.	14	Left dorsal, right lumbar	68	68	60
18. G. G.	13	Right dorsal, left lumbar	78	30	30
19. A. R.	20	Right dorsal, left lumbar	46	70	65
20. M. D.	22	Right dorsal, left lumbar	35	92	86
21. R. F.	23	Left dorsal, right lumbar	61	12	12
22. P. M.	20	Left dorsal, right lumbar	71	60	60
23. J. T.	19	Kyphosis	42	50	50
24. J. H.	25	Right dorsal, left lumbar	36	95	100
25. M. N.	14	Right dorsal, left lumbar	52	120	120
26. L. P.	18	Right dorsal, left lumbar	64	30	30
27. L. K.	19	Right dorsal, left lumbar	47	116	110
28. R. McN.	14	Funnel chest	47	70	72
29. E. S.	15	Left dorsal, right lumbar	85	60	58
30. M. C.	25	Right total	97	62	60
31. B. G.	14	Kyphosis	82	68	56
32. N. G.	17	Left dorsal, right lumbar	90	48	36
33. A. R.	23	Right dorsal, left lumbar	53	92	90
34. A. P.	14	Left dorsal, right lumbar	28	44	66
35. J. C.	22	Left dorsal, right lumbar	37	55	55
36. H. E.	20	Left dorsal, right lumbar	100	70	66
37. I. A.	22	Right dorsal, left lumbar	65	90	90
38. A. B.	19	Left dorsal, right lumbar	45	40	50
39. D. P.	15	Left dorsal, right lumbar	68	15	30
40. F. R.	20	Right dorsal, left lumbar	66	78	70
41. M. McN.	12	Left dorsal, right lumbar	47	52	50
42. P. DeN.	15	Right dorsal, left lumbar	40	60	90
43. M. McK.	41	Right dorsal, left lumbar	52	50	60
44. R. DeP.	8	Funnel chest	42	30	30
45. N. C.	17	Right dorsal, left lumbar	91	58	38
46. L. G.	13	Right dorsal, left lumbar	61	120	115
47. J. M.	18	Right dorsal, left lumbar	40	50	60
48. C. S.	17	Left dorsal, right lumbar	69	56	62
49. A. B.	22	Left total	97	56	60
50. A. S.	14	Left dorsal, right lumbar	90	55	70
51. E. W.	20	Right dorsal, left lumbar	61	65	57
52. B. P.	10	Right dorsal, left lumbar	72	55	55
53. B. M.	30	Left dorsal, right lumbar	115	18	30
54. M. S.	17	Right dorsal, left lumbar	66	68	63
55. N. W.	57	Left dorsal, right lumbar	30	−12	−12
56. M. K.	24	Right dorsal, left lumbar	57	70	70
57. A. K.	15	Right dorsal, left lumbar	75	110	105
58. J. N.	14	Right dorsal, left lumbar	82	90	90
59. E. K.	19	Left total	49	62	40

also for pulmonary fibrosis or emphysema that might be detected by this procedure. The limitations of roentgenologic examination of the heart in chest deformities must, however, be kept in mind.

After exclusion of heart and lung disease by the patient's history, physical examination, and roentgenologic observations, the vital capacity was measured and the electrocardiogram was taken. The standard limb leads and chest leads CF_2, CF_4, and CF_5 in the sitting and recumbent positions were recorded on each patient.

RESULTS

The observations that we made from the routine examination of these selected patients are as follows:

There were seventeen patients with an electrical axis of between 80 and 95 degrees toward the right, two patients with left axis deviation, and eighty-one patients, the great majority, with a normal electrical axis (Table I).

When the axis was studied in persons with a marked decrease in the vital capacity, the percentages changed slightly. Thirty-two patients with less than 50 per cent of normal vital capacity were observed from this point of view, and the distribution was as follows: 25 per cent toward the right, 3.4 per cent toward the left, and 71.6 per cent normal. We did not find a close relationship between the vital capacity and the electrical axis. In the group with less than 50 per cent of normal vital capacity, with the proportion of right axis deviation slightly increased, we found one case with 38 per cent of normal vital capacity and an axis of 32 degrees, and in another, with 30 per cent of normal vital capacity, the axis was –12 degrees.

Then we tried to correlate the electrical axis with the curve of the spine. There were sixty-seven patients with right dorsal, left lumbar scoliosis (Group 1), nineteen with left dorsal, right lumbar scoliosis (Group 2), five with the convexity entirely to the left (Group 3), one with the convexity entirely to the right (Group 4), six patients with predominant kyphosis (Group 5), and two with funnel chest (Group 6).

In our first group, 26.8 per cent of the patients had deviation toward the right and 73.2 per cent were normal. There were none with deviation toward the left. In the second group, 15.6 per cent were toward the left and 84.4 per cent were normal. There were none toward the right. In the third group we found 100 per cent with normal axes. In the fourth, the only patient in the group had a normal axis. In the fifth group (kyphosis) there were 100 per cent with normal axes, and in the last group both patients had normal axes.

Because we observed that in thirty-one instances the axis shifted toward the right instead of to the left when the patients changed from the sitting position to recumbency, we tried to correlate these observations with the type of the deformity, but we did not find any relationship with either the build or the vital capacity of the patients.

twenty-three cases (six males and seventeen females). Among these patients, nine were less than 15 years old and fourteen were 15 years or more. The mean age was 16.3 years. The observations were as follows: T in CF_2 inverted seven times in the sitting position and seventeen times in recumbency; T in CF_4 inverted three times in the sitting position and three times in recumbency; T in CF_5 inverted twice in the sitting position and once in recumbency.

The following are the histories and electrocardiograms of two interesting patients.

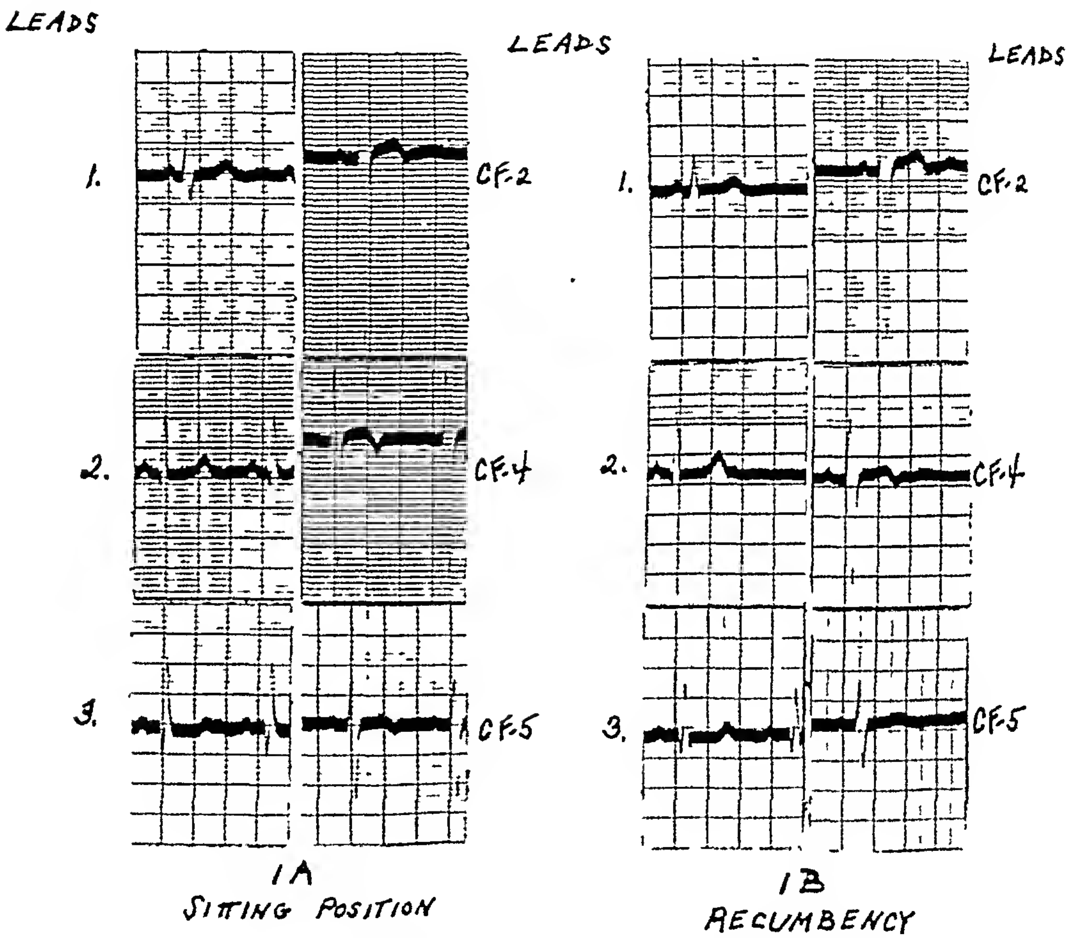

Fig. 1.—Electrocardiograms of Case 1, E. S.

Case 1.—The first, E. S., was a 15-year-old schoolgirl who came to the hospital with the chief complaint of deformity of the chest. This abnormality was first noted when she was 5 years old. Her mother therefore took her to the Children's Hospital in Boston, where roentgenologic studies revealed one hemidorsal vertebra causing scoliosis. The patient was treated for a number of years with exercises, and has recently been placed in a plaster cast.

Past History.—Measles and chicken pox. No other disease. No history of rheumatic fever. No operations. Very active and athletic. No cardiac, respiratory, or gastrointestinal complaints.

Family History.—No family history of any similar or other deformity.

TABLE I—CONT'D

NUMBER	AGE (YR.)	TYPE OF DEFORMITY	VITAL CAPACITY (PER CENT OF NORMAL)	AXIS SITTING DEGREES	AXIS RE-CUMBENT DEGREES
60. A. C.	19	Right dorsal, left lumbar	65	90	90
61. E. G.	14	Right dorsal, left lumbar	59	56	42
62. E. S.	14	Right dorsal, left lumbar	80	81	78
63. A. D.	15	Right dorsal, left lumbar	81	75	82
64. R. W.	15	Kyphosis	26	76	76
65. R. M.	18	Right dorsal, left lumbar	29	43	41
66. H.H.	21	Right dorsal, left lumbar	75	55	53
67. M. D.	39	Right dorsal, left lumbar	30	30	20
68. R. C.	16	Right dorsal, left lumbar	72	72	55
69. I. S.	13	Left dorsal, right lumbar	93	30	40
70. A. B.	17	Right dorsal, left lumbar	88	87	90
71. G. M.	26	Right dorsal, left lumbar	89	18	48
72. H. B.	13	Right dorsal, left lumbar	47	70	55
73. L. B.	13	Right dorsal, left lumbar	45	55	55
74. Y. T.	17	Right dorsal, left lumbar	73	70	74
75. G. F.	22	Kyphosis	62	85	70
76. L. L.	22	Right dorsal, left lumbar	56	40	62
77. E. P.	22	Right dorsal, left lumbar	49	50	60
78. A. C.	35	Right dorsal, left lumbar	71	48	53
79. J. F.	20	Right dorsal, left lumbar	43	82	80
80. M. O'C.	15	Left total	84	30	30
81. H. R.	23	Right dorsal, left lumbar	94	6	6
82. F. D.	14	Kyphosis	110	76	82
83. C. S.	12	Right dorsal, left lumbar	54	30	30
84. P. N.	14	Right dorsal, left lumbar	93	78	70
85. A. H.	17	Right dorsal, left lumbar	80	19	79
86. M. F.	17	Right dorsal, left lumbar	84	52	58
87. E. St. I.	14	Right dorsal, left lumbar	83	66	73
88. M. O'C.	39	Right dorsal, left lumbar	73	38	45
89. P. K.	16	Left dorsal, right lumbar	107	-3	-18
90. B. H.	15	Right dorsal, left lumbar	62	113	108
91. L. P.	20	Right dorsal, left lumbar	30	30	36
92. B. F.	17	Left dorsal, right lumbar	59	68	56
93. A. D'E.	22	Right dorsal, left lumbar	86	27	30
94. E. K.	16	Right dorsal, left lumbar	93	90	80
95. J. O.	18	Left dorsal, right lumbar	93	38	49
96. V. O.	13	Right dorsal, left lumbar	57	50	42
97. R. L.	17	Right dorsal, left lumbar	95	75	70
98. H. P.	23	Right dorsal, left lumbar	94	35	40
99. M. T.	16	Right dorsal, left lumbar	83	41	45
100. C. M.	11	Right dorsal, left lumbar	59	66	72

In considering the P wave, we observed that this deflection was either peaked or notched, or both at the same time, in thirty-two instances in Lead II, in five in Lead I, and in nineteen in Lead III. The height was no more than 2 or 3 mm., but the shape was very similar to that of the P waves in mitral stenosis or congenital heart disease.

With regard to the QRS deflection, we noticed that, in spite of the duration, which was not more than 0.10 second, it was frequently slurred or notched; the height was more than 5 mm. in the limb leads and 10 mm. in the chest leads.

In the S-T segments no significant changes were found.

So far as the T waves are concerned, nothing abnormal was found in the limb leads. In the chest leads the T waves were inverted in

Past History.—Only chicken pox. No history of rheumatic fever. Rare sore throat. For several years he had had slight dyspnea on exertion, without cough or hemoptysis.

Family History.—Irrelevant.

Physical Examination.—Patient had a marked left dorsal scoliosis, with marked high thoracic kyphosis. *Heart:* apex impulse felt in fifth intercostal space, 1 cm. inside the midclavicular line. Sounds regular, of good quality. No murmurs. The pulmonary second sound was louder than the aortic second. Blood pressure, 123/75. Lungs negative. Liver not tender and apparently not enlarged. Roentgenologic examination showed nothing particularly wrong with the heart.

At this time a spinal fusion was performed, and since then has become stabilized.

An electrocardiogram in the sitting position (Fig. 2, *A*) revealed normal rhythm, a rate of 58, a P-R interval of 0.18 second, slight elevation of S-$T_{1,2}$, upright and pointed $T_{1,2}$, and a rather isoelectric T_3. In the chest leads there were an inverted T in CF_2, a diphasic T in CF_4, and an upright T in CF_5. In recumbency, T_1 became lower and T_3 higher, the T in CF_2 and CF_4 more deeply inverted, and the T in CF_5 upright (Fig. 2, *B*).

DISCUSSION

The deviation of the axis according to the type of the spinal curvature can be explained by the roentgenograms which we observed in our patients. We have seen that, with right convex scoliosis, the heart is shifted to the left and the left border appears straightened, which Roesler calls "mitral configuration." With the less frequent left convex scoliosis, the heart is shifted to the right and the aortic shadow appears widened. The same picture, but less marked, was presented by the patients with right total, and left total, curvature, respectively. In kyphosis we did not find any striking difference from the normal, although sometimes the heart lay in a horizontal position. We made out no abnormality in the roentgenograms in our cases of funnel chest. Nevertheless, in two cases especially, which we do not discuss here because of associated congenital heart disease and probable arachnodactyly, there was a very marked shift of the heart toward the left.

The great preponderance of cases of normal axis in scoliosis can be explained by (1) displacement of the whole heart without rotation on its anteroposterior or longitudinal axis, such as is likely to occur in funnel chest, or (2) rotation around the longitudinal axis, which could compensate for the rotation around the anteroposterior axis. The effect of rotation of the heart about the longitudinal axis has been studied by two groups of investigators. Boden and Neukirch[23] found that rotation of the isolated perfused heart about the long axis to the left resulted in a tendency to right preponderance, whereas rotation to the right gave opposite effects. On the other hand, Meek and Wilson[24] found that displacement of the heart to the right or the left usually caused a combined rotation on both axes, and produced electrocardi-

Physical Examination.—Well-developed girl with a conspicuous left dorsal scoliosis. The right lumbar scoliosis was not very marked. Her reflexes were normal. The heart was not enlarged and there were no murmurs. Blood pressure, 110/70. Lungs normal.

An electrocardiogram in the sitting position (Fig. 1, *A*) revealed slight sinus arrhythmia, an average rate of 80, a P-R interval of 0.14 second, normal axis, prominence of S_1 and Q_3, slight late sagging of $S\text{-}T_3$, and upright T waves in Leads I, II, and III. In the chest leads there were diphasic T waves in CF_2 and late inversion of the T waves in CF_4 and CF_5. In recumbency the electrocardiogram (Fig. 1, *B*) showed marked sinus arrhythmia and an average rate of 75. S_1 had disappeared and Q_3 was not nearly so prominent. The T waves in Leads II and III had become more upright and pointed. In the chest leads, T in CF_2 had become more upright, T in CF_4 less inverted, and T in CF_5 upright.

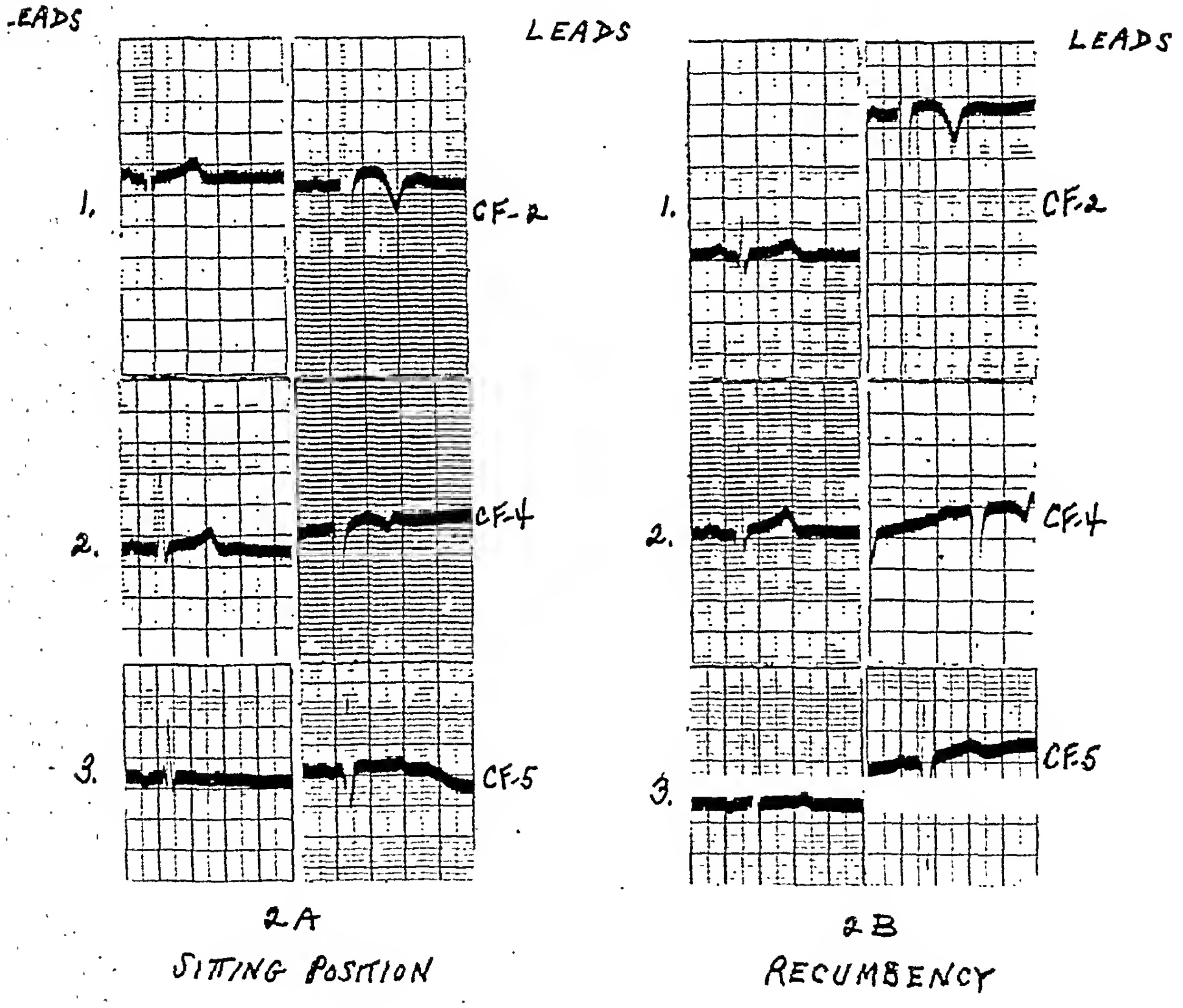

Fig. 2.—Electrocardiograms of Case 2, J. T.

CASE 2.—In January, 1942, a 19-year-old, single man, J. T., was admitted to the hospital because of curvature of the spine. This curvature was first noted at the age of 10 years, and had become progressively worse. He entered because of attacks of pain in the lower right chest region for three years, pain which was sharp and shooting in nature.

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ographic changes which cannot be predicted because of the opposing effects of simultaneous rotation around the longitudinal and anteroposterior axes.

So far as the literature about cases of pulmonocardiac failure as a result of spinal deformities is concerned, the frequency of right axis deviation is much higher than in our series, which is presented without regard to the type of curvature. It is logical to believe that the atelectasis, sclerosis, and superimposed infections which frequently supervene in these cases of long standing throw an increasing strain on the right side of the heart, producing a tendency of the axis to lean toward the right. Thus, the real axis produced by the deformity itself is overlapped by the additional factors which finally give the picture of chronic cor pulmonale. The high proportion of inverted T waves in Lead CF_2 in our cases can be explained by the fact that we have more cases with right dorsal, left lumbar scoliosis; this increases the possibility that we actually have the CF_1 pattern, instead of CF_2, in spite of the standard location of electrodes.

SUMMARY AND CONCLUSIONS

We have carried out electrocardiographic studies in one hundred cases of chest deformity without evident cardiac or pulmonary disease.

The results were as follows:

1. In right dorsal, left lumbar scoliosis, right axis deviation was present in 26.8 per cent of the cases, and a normal axis in 73.2 per cent.
2. In left dorsal, right lumbar scoliosis, left axis deviation was present in 15.6 per cent of the cases, and a normal axis in 84.4 per cent.
3. In total left or right scoliosis, in kyphosis, and in funnel chest, all the patients presented a normal axis.

The great percentage (80 per cent) of normal axes in the whole group is explained either by a total displacement of the whole heart, without rotation, or by combined rotation on both longitudinal and anteroposterior axes, with neutralization because of their opposing effects.

The T waves were normal in limb leads but inverted in a minority of the cases in the precordial leads, varying somewhat with the position of the patient; this is to be ascribed, in part at least, to the unusual relationship of heart position to the external landmarks of the thorax.

The authors would like to express their appreciation to Miss Deborah Hanson and Miss Louise Wheeler of the Cardiac Laboratory of the Massachusetts General Hospital for their help in the preparation of this paper.

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TABLE I

DIFFERENT GRADES OF ABERRATION IN 525 TYPES OF AURICULAR PREMATURE SYSTOLES (APS)

NO ABERRATION AT ALL	NO ABERRATION OF QRS, BUT ABERRATION OF RS-T SEGMENT OR T WAVE	FIRST DEGREE ABERRATION							SECOND DEGREE ABERRATION (TWO FEATURES OF QRS CHANGED)	THIRD DEGREE ABERRATION (THREE FEATURES OF QRS CHANGED)	FOURTH DEGREE ABERRATION (FOUR FEATURES OF QRS CHANGED)	BLOCKED APS	TOTAL
		QRS CHANGED IN AMPLITUDE ONLY	QRS CHANGED IN DIRECTION ONLY	QRS CHANGED IN DURATION ONLY	QRS CHANGED IN CONFIGURATION ONLY	R TALLER, S SMALLER OR VICE VERSA	R THE SAME, S DEEPER OR S THE SAME, R TALLER	DIFFERENCE IN SIZE OF Q ONLY					
137	42	79	0	10	42	33	2	13	86	45	28	8	525

AURICULAR PREMATURE SYSTOLE

I. Aberration of the Ventricular Complex in the Electrocardiogram

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Auricular premature systoles are characterized, in the electrocardiogram, by premature auricular (P) waves of abnormal contour. Their ventricular deflections (QRS-T complexes) may be identical with those of the normal beats or may differ from them. If they differ, we speak of "aberration." The term was introduced by Lewis,[1] and the abnormality of the ventricular complexes was attributed by him "to deficient conduction along certain tracts of the junctional tissues."[2] The literature contains no satisfactory explanation of aberration, and, in general, little importance has so far been attached to it. It seemed to us that so tangible an electrocardiographic finding might have greater significance. It might, for instance, be found to reflect definite pathologic changes in the heart; in that event, it would yield information not heretofore obtainable from the electrocardiogram. With that possibility in mind, we decided to study the phenomenon of aberration. Our investigation aims at establishing its relative frequency and some of the factors which determine its occurrence. It includes a correlation of clinical and electrocardiographic observations. This correlation attempts to demonstrate the clinical significance of aberration.

MATERIAL AND METHOD

The electrocardiograms of 201 patients were collected. Each electrocardiogram consisted of the three standard leads and one chest lead, IVF, except for 76 older electrocardiograms in which no chest lead was taken. In two cases, on the other hand, two chest leads, CF_2 and CF_4, were taken. The length of each lead strip was 25 centimeters. Many patients exhibited APS* in more than one record, but only one record was used for analysis (except in the clinical part of our study). Each electrocardiogram was first interpreted; next, a count of the number of APS per lead was taken; then, each APS was analyzed as to the degree of prematurity (its location in relation to the preceding normal beat). The following terminology was introduced for purposes of classification:

Location I (late APS): The P wave of the APS does not touch the T wave of the preceding beat (Fig. 2, *A* and *B*; Fig. 11, *B*, x_2).

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Received for publication June 24, 1944.

*APS will be used as an abbreviation for auricular premature systole throughout this paper.

frequent than APS without aberration. Besides being rarer, APS without aberration are also more easily overlooked (Fig. 2). They may be particularly inconspicuous if all the P waves of the respective lead are of low amplitude. Furthermore, they may occur late in diastole and may then be so spaced that the distance from the preceding normal beat looks almost normal (Fig. 2, A). In other cases, the disturbance of

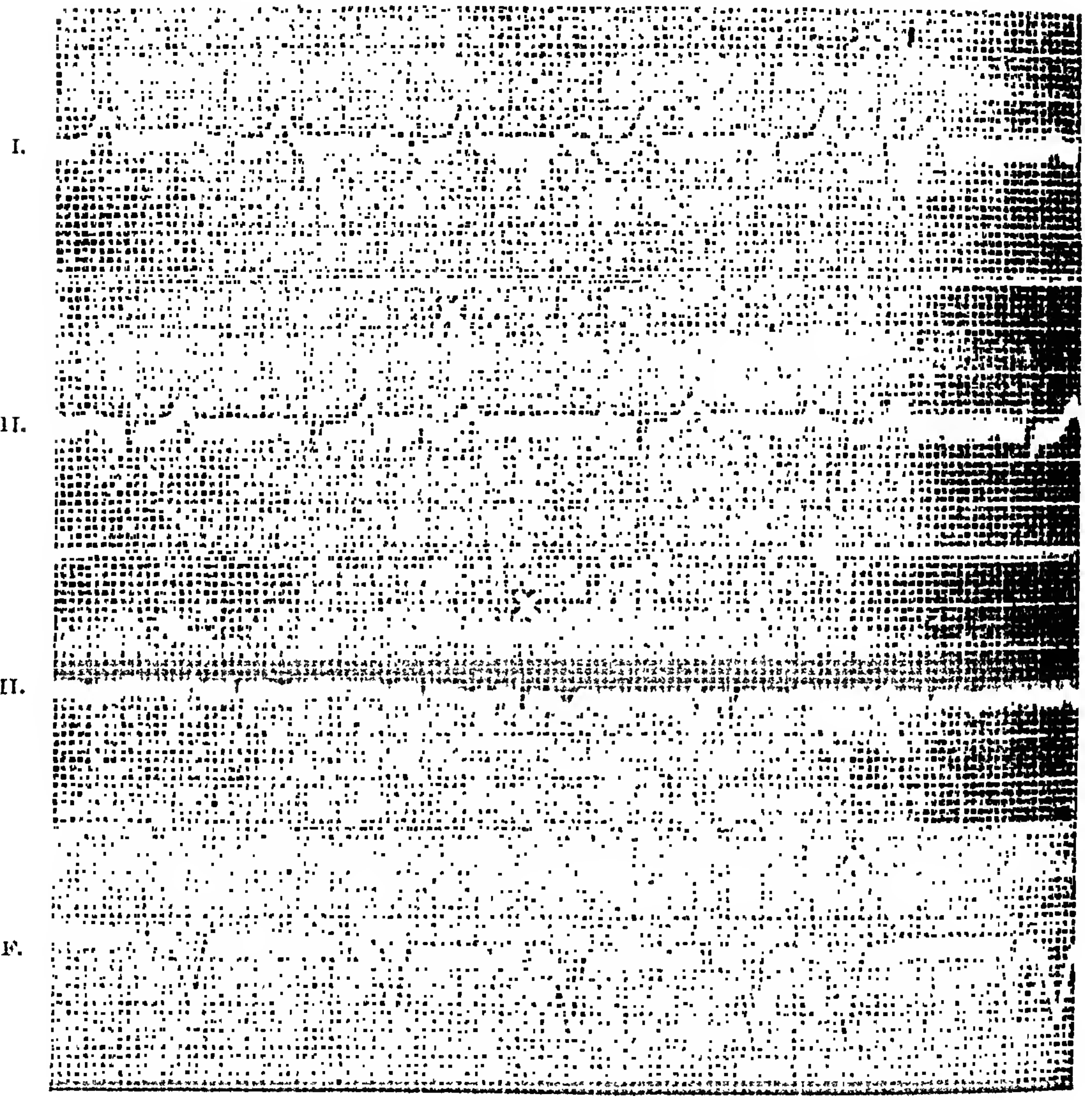


Fig. 1.—A four-lead electrocardiogram. Aberration of the APS is most marked in the chest lead.

rhythm may be easily recognized, but may be misinterpreted as sinus arrhythmia (Fig. 3).*

Aberration of RS-T or of T Only (Fig. 4).—The QRS complexes of APS may be identical with those of the normal beats, but the RS-T seg-

*Sinus arrhythmia is the result of an increase in vagal tone; the development of APS also appears to be favored by an increase in vagal tone. Sinus arrhythmia and APS may, therefore, coexist. If such APS lack aberration, the differentiation between the two conditions may be difficult. In that case it may be advisable to take several chest leads; in one of the chest leads, the ventricular complexes, or the T waves only, may show aberration, and thus establish the diagnosis of APS.

Location II (fairly late APS): The P wave of the APS barely touches the descending limb of the T wave of the preceding beat (Fig. 1; Fig. 11, *B*, x_1).

Location III (moderately early APS): The P wave of the APS is superimposed on the descending limb of the preceding T wave (Fig. 2, *C*; Fig. 8, *C*).

Location IV (early APS): The P wave of the APS is superimposed on the ascending limb of the preceding T wave (Fig. 9, *B*; Fig. 11, *A*, x_2).

Location V (very early APS): The P wave of the APS is superimposed on the preceding RS-T segment close to the QRS complex (Fig. 8, *A*).

Twenty-nine records exhibited only one APS per record. One hundred seventy-two, however, showed two or more APS per record. Of the latter, twenty-two showed that all of the APS were of the same location. These APS were classified by us as being of one and the same type. One hundred fifty records showed multiple APS of varying location, and these were classified by us as APS of different types. To give an example: If one record contained three APS, one of location I, another of location III, and a third of location V, the APS were classified as of three different types. The total number of APS counted by us was 1,306; the number of different types found was 525.

Our patients varied in age from 2 to 83 years. Thirty-six patients died during the period of observation; post-mortem examinations were performed on thirteen of these. The clinical charts of all patients were analyzed for diagnosis, and evidence of cardiovascular disease, if found, was carefully noted.

Frequency of Aberration.—The literature contains conflicting statements concerning the frequency of aberration. White,[3] White and Stevens,[4] and Carter[5] estimate that "about half the cases that show auricular premature beats show also varying abnormality of spread of excitation wave through the ventricle." Pardee,[6] on the other hand, states that the ventricular complexes of auricular premature systoles are "*always* slightly different from the other ventricular complexes of the record," and he points out that "this difference is evident in records showing the auricular premature beats in three leads; the curve may be but little changed in any one lead, and yet quite a variant in the other two." Our own observations show definitely that aberrant ventricular complexes are much more frequent than normal ones. Of our 525 different types of APS, eight were blocked, i.e., they had no ventricular complexes at all. Of the remaining 517 types, 137, only a little more than one-fourth, showed no aberration at all (Table I). The figure 137 would have been still smaller, and the percentage of APS showing aberration still greater, if all of our records had included one or more chest leads. This would have been so for two reasons: first, with a larger number of leads the probability that aberration would appear would have been greater;[6] second, chest leads, as such, often magnify aberration, and thereby aid in recognizing it (Fig. 1). In any event, our analysis shows that APS with aberration are much more

The most frequent single change was increase or decrease in the amplitude of QRS (Fig. 6, *A*). It occurred, unaccompanied by other changes, in 79 of the 517 types of APS. The increase or decrease in height was usually slight, yet greater than the amplitude variations of normal beats; it often greatly aided in the recognition of the APS. In the chest leads, amplitude variations of APS were usually greater than in the limb leads. Very marked amplitude changes rarely occurred alone, but were usually associated with changes in the duration, configuration, or direction of the QRS complexes. Frequently the total amplitude was the same as that of the normal beats, but the R waves were lower and the S waves deeper, or the R waves taller and the S waves less deep; this occurred as the only aberration in 35 of 517 types.

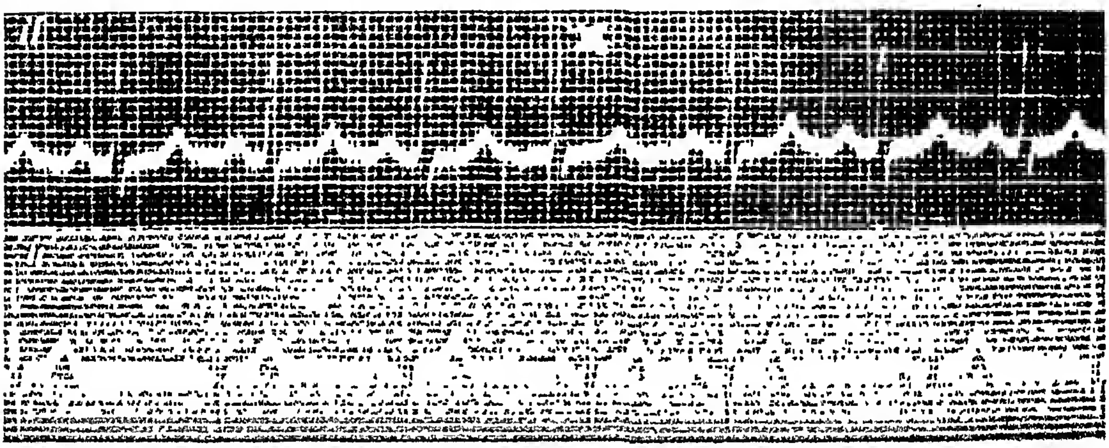


Fig. 3.—APS simulating sinus arrhythmia (two cases).

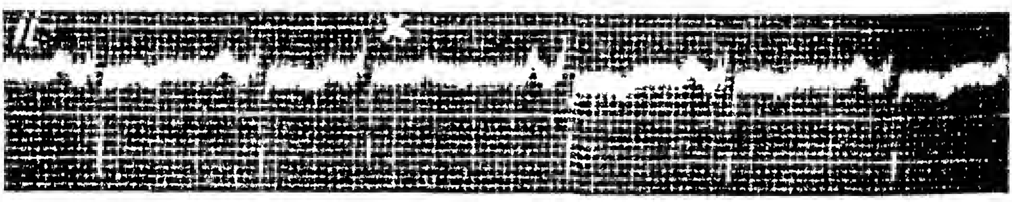


Fig. 4.—An APS with aberration limited to the RS-T segment and T wave.

Changes in the direction of QRS were never found alone, but always in conjunction with changes in amplitude, duration, or configuration, which produced the more marked degrees of aberration (Fig. 6, *B*).

Changes in the duration of the QRS complex were seldom found alone, viz., in only ten of 517 types, and were then usually minor (Fig. 6, *C*). The major changes in duration again were found only in conjunction with changes of amplitude, configuration, or direction.

Changes in configuration were more common (Fig. 6, *D*). Slurring or notching in the QRS complex of the APS as the only sign of aberration occurred in 42 of the 517 types. The more marked degrees of slurring or notching were usually associated with other changes, especially with changes in amplitude, or with changes in amplitude, duration, and

ments or the T waves, or both, may be aberrant. In our series, 43 of the 517 types showed this form of limited aberration. Not infrequently, the aberration of the T waves presented itself in the chest lead only, which is probably due to the fact that in chest leads all T waves are usually larger, and deflections of the RS-T segment are normally more pronounced than in the limb leads (Fig. 5). The more widespread use of multiple chest leads will undoubtedly increase the number of APS discovered electrocardiographically.

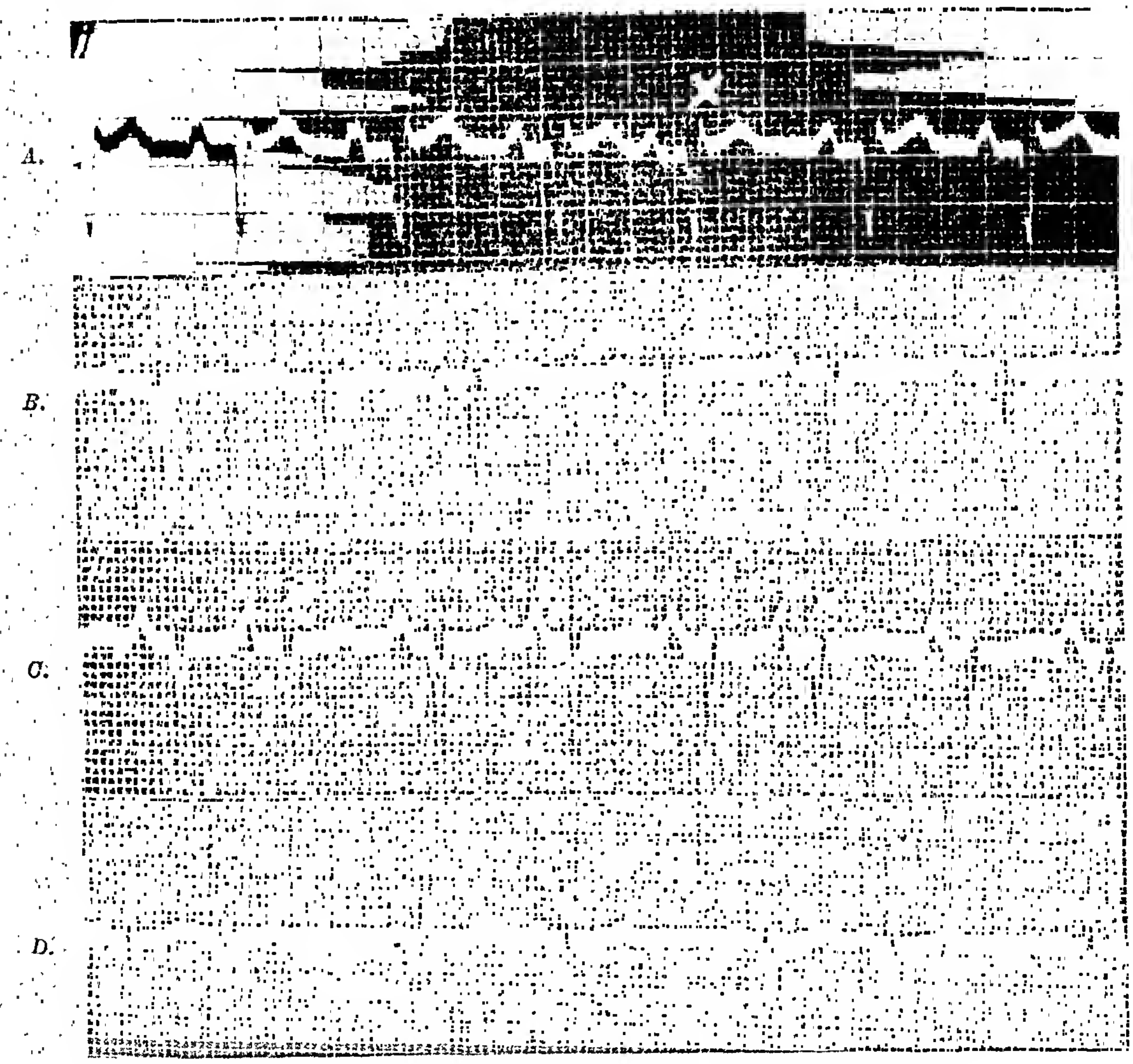


Fig. 2.—APS without any aberration (four cases).

The T-wave aberration in limb leads or chest leads consisted of an increase or decrease in the size of the T wave, a change in its shape, rarely a change in its direction, or a combination of these changes, with or without elevation or depression of the RS-T segment.

Aberration of QRS.—In the majority of APS, 337 of the 517 types, aberration of the QRS complexes was present. This varied in degree from slight changes in amplitude to marked changes in height, duration, configuration, and direction, resulting in truly bizarre complexes. Aberration of QRS was, as a rule, associated with aberration of T, and there was usually parallelism in the degree of both changes.

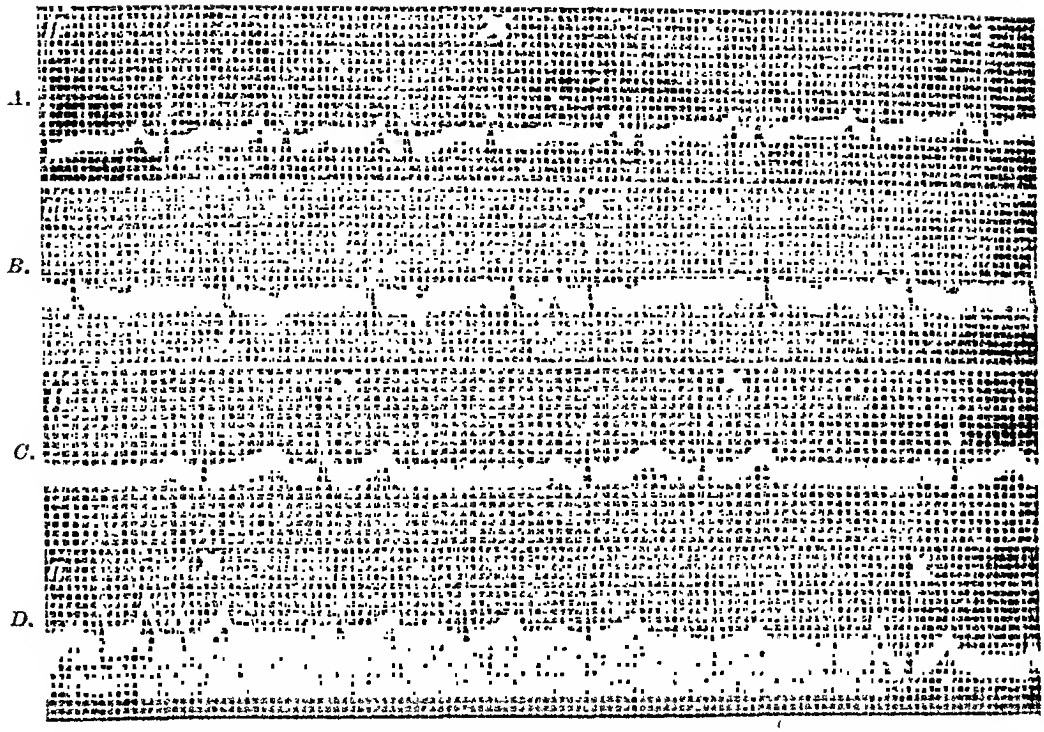


Fig. 6.—First and second degree aberration of APS (four cases). *A*, Change in amplitude of QRS (first degree aberration). *B*, Change in direction of QRS, here accompanied by a change in configuration (second degree aberration). *C*, Change in duration of QRS (first degree aberration). *D*, Change in configuration of QRS (first degree aberration).

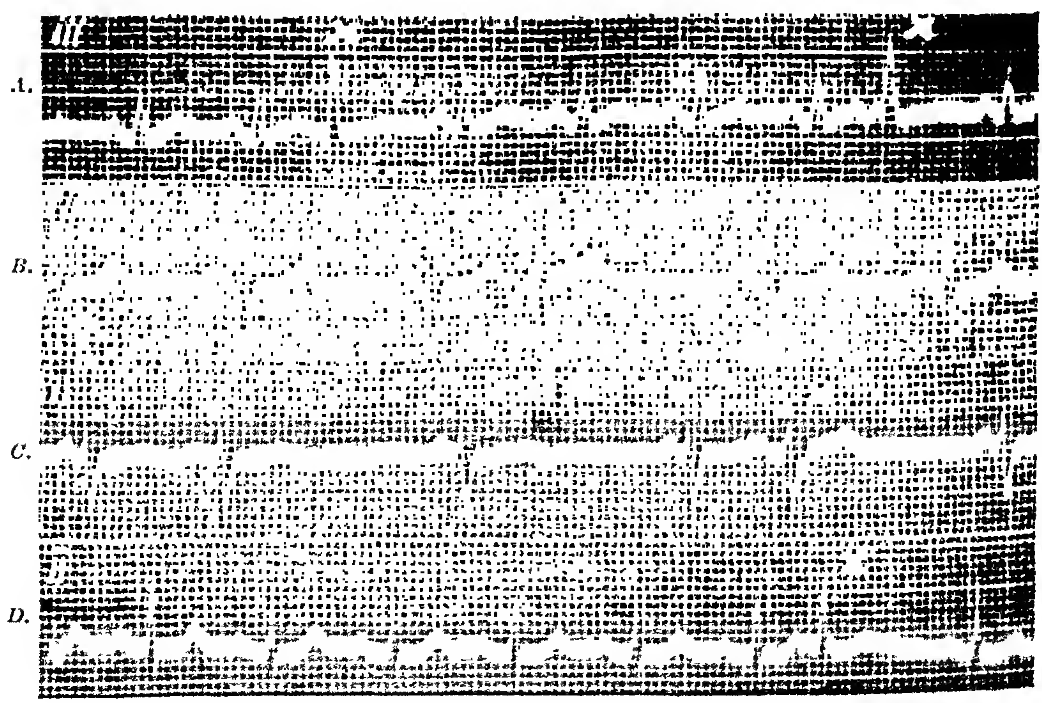


Fig. 7.—Second degree aberration of APS (four cases). *A*, Change in amplitude and configuration of QRS. *B*, Change in amplitude and duration of QRS. *C*, Change in duration and configuration of QRS. *D*, Change in configuration of QRS; besides, R is of higher, S of lower, amplitude.

direction. Another change in configuration occasionally found was the appearance (or disappearance) of a Q wave. This occurred as the *only* demonstrable aberration in 13 of 517 types.

Higher Degrees of Aberration.—The higher degrees of aberration were less frequent than the lower (Table I). For purposes of comparison we grouped all types of APS with only *one* kind of change,

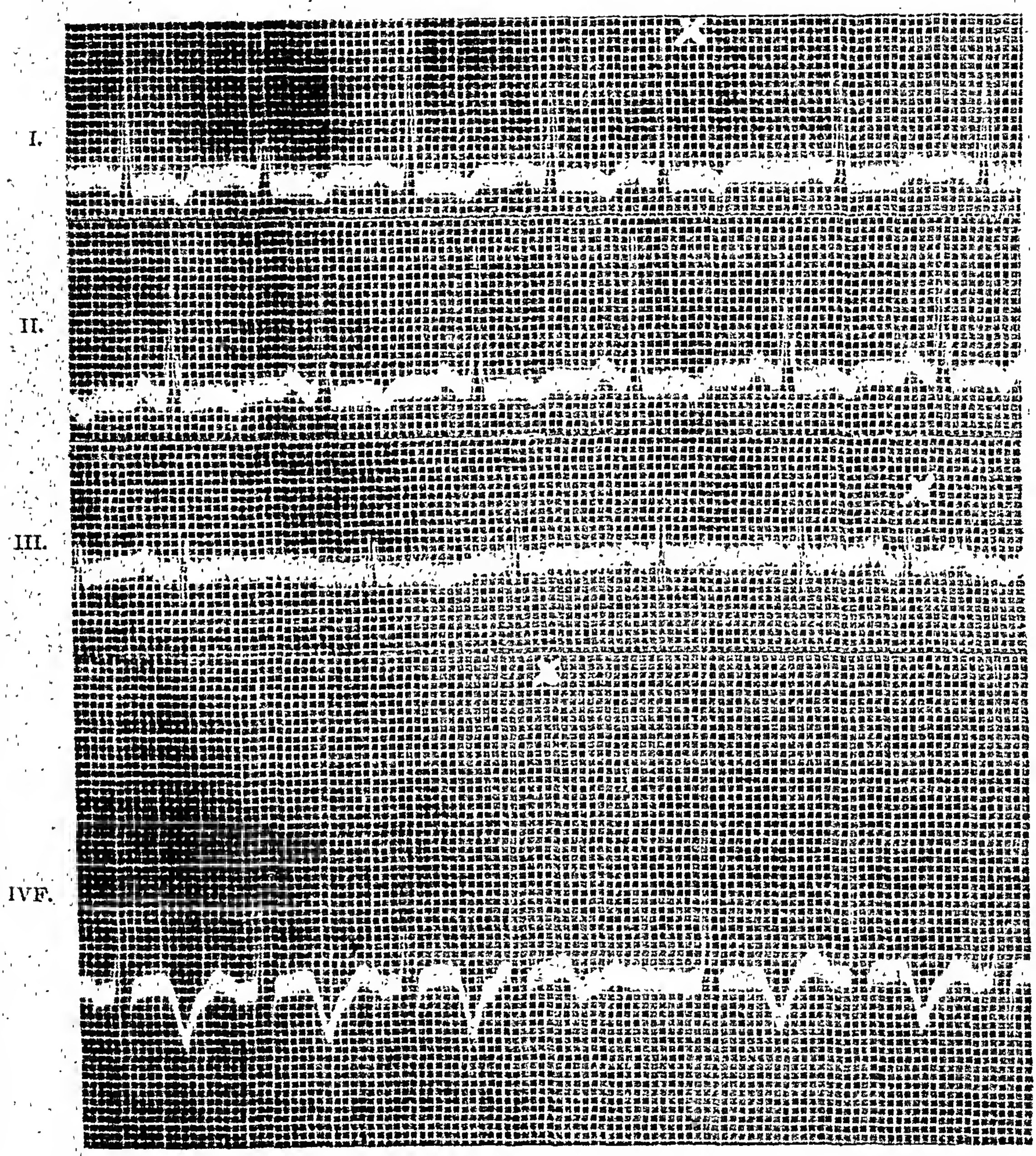


Fig. 5.—A four-lead electrocardiogram. Little aberration of the APS in the limb leads, definite aberration in the chest lead.

either amplitude, duration, or configuration, and called the group "first degree aberration." There were 179 types in this group. The group "second degree aberration" (Fig. 7), which was characterized by two changes, namely, amplitude *and* configuration, comprised 86 types. The next group, "third degree aberration" (Fig. 8), with a combination of three changes, namely, amplitude, configuration, and direction, was still

10) increases the likelihood that these APS may be mistaken for ventricular premature systoles (VPS).* The distinction between such APS and VPS may be of more than academic importance. For one thing, the patient may be receiving digitalis, and the mistaken interpretation of the bizarre APS for VPS may lead to the suspicion of toxic digitalis effect. That suspicion would not arise if the auricular origin of the bizarre premature systoles were recognized, for digitalis does not cause APS. A second, and equally serious error may result if bizarre APS coexist with VPS. In that case, a bizarre APS may simulate a VPS arising from a different focus. Since multifocal VPS indicate myocardial damage, the misinterpretation may lead to a wrong diagnosis (Fig. 10).

A.

B.

C.

D

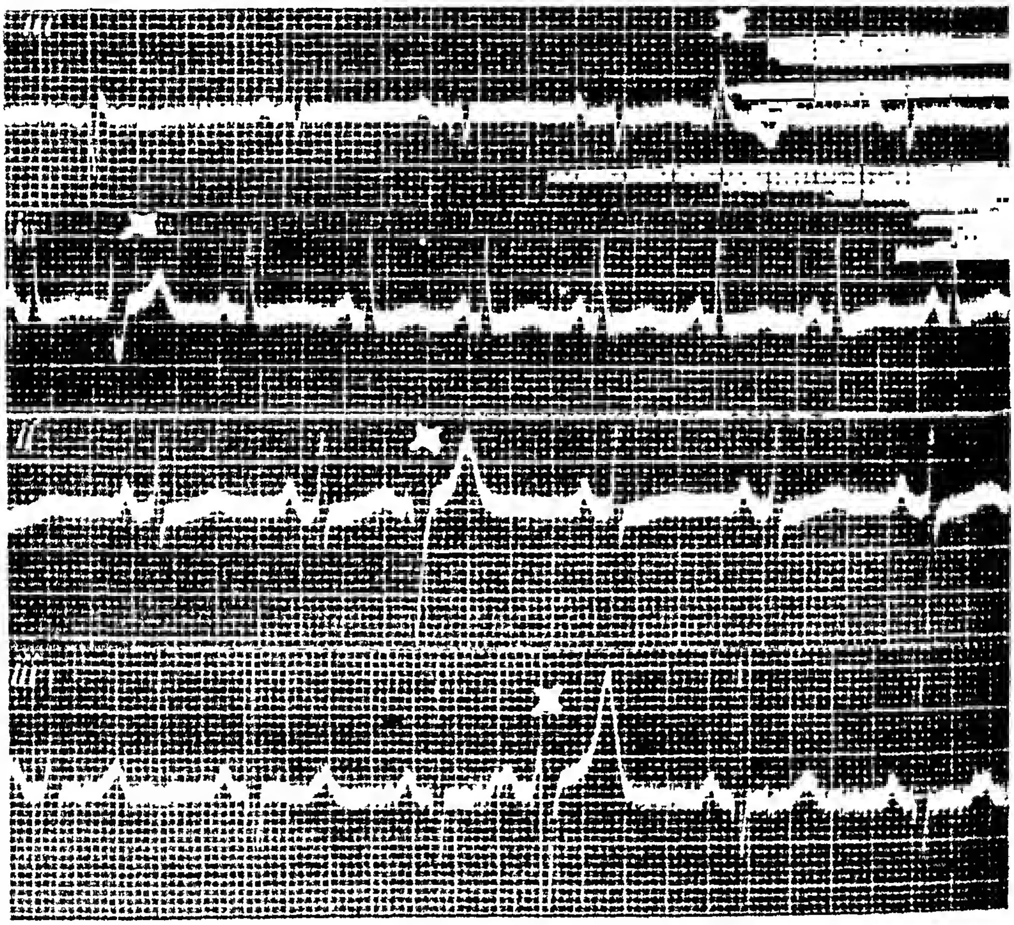


Fig. 9.—Fourth degree aberration of APS (four cases). All four characteristics of QRS are changed. Such bizarre APS are likely to be mistaken for VPS.

Conflicting Opinions on the Cause of Aberration.—The cause of aberration is still obscure, and the literature contains conflicting statements regarding its mechanism. It seems an established fact that the change in the QRS complex depends upon abnormal spreading of the contraction. Lewis[1] states: "The changed form of the ventricular

*VPS will be used as an abbreviation for ventricular premature systole throughout the remainder of this paper.

smaller (45 types), and the group "fourth degree aberration" (Figs. 9 and 10) was the smallest of all, consisting of only 28 types. This group was in many ways the most interesting. In these APS, the amplitude, duration, configuration, and direction of QRS were different from those of the normal beats. Aberration of the T wave, as a rule, was correspondingly marked, although reversal of the direction of T was seen only twice. The QRS complexes of this group are likely to be as wide and notched as those of bundle branch block. Compared to the QRS complexes of the normal beats, they often appear so bizarre that

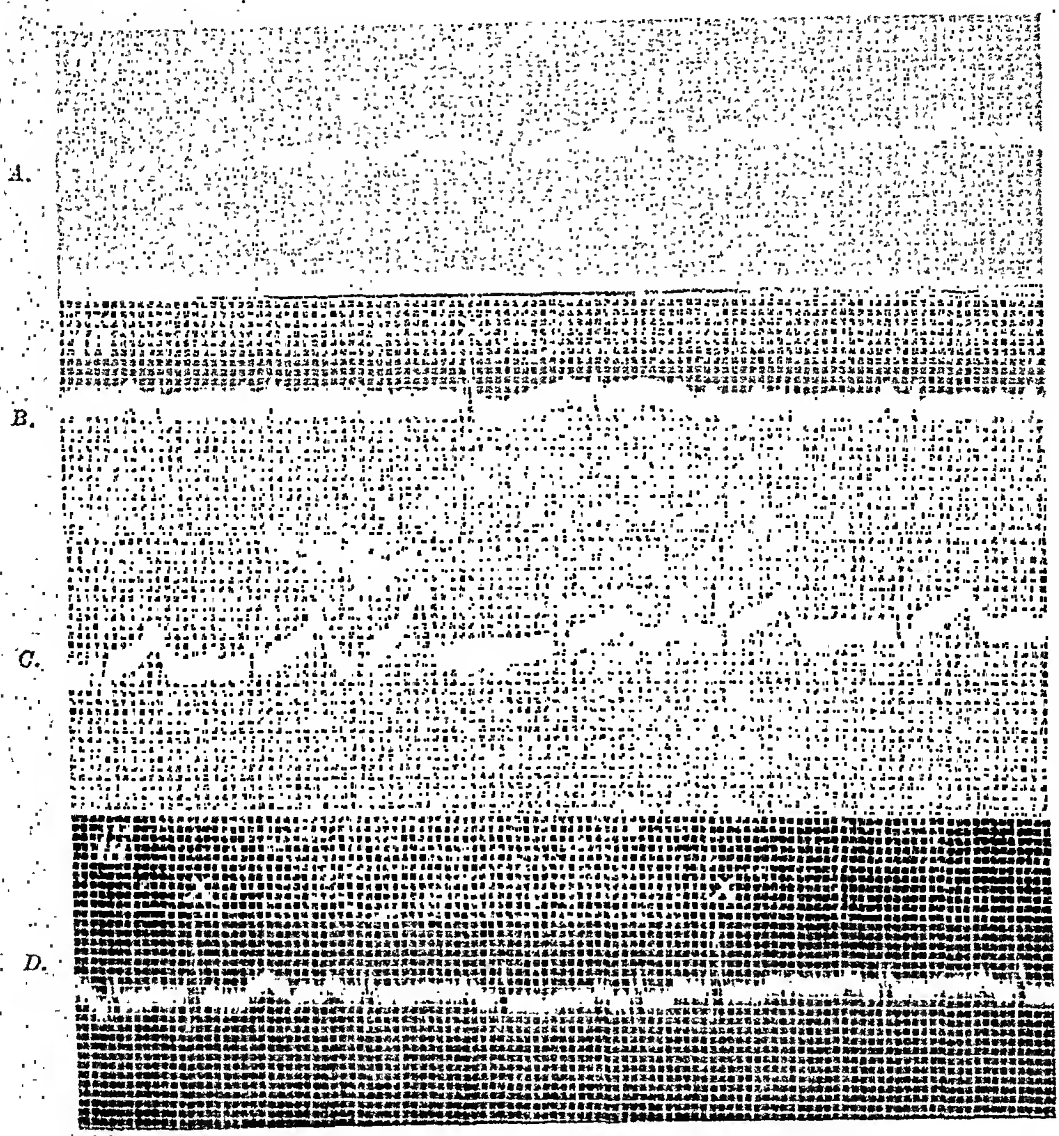


Fig. 8.—Third degree aberration of APS (four cases). *A*, *B*, and *D*, Change in amplitude, duration, and configuration of QRS. *C*, Change in amplitude, direction, and configuration of QRS.

the APS are commonly mistaken for premature systoles of ventricular origin. These QRS complexes are, of course, preceded by abnormal premature P waves. In all but two instances, however, the APS with "fourth degree aberration" occurred so early in diastole that their P waves were superimposed on the preceding T waves, on either the downstroke or the upstroke. Such inconspicuousness of the P waves (Fig.

ascribes aberration to asynchronous stimulation of the ventricles resulting from the abnormal way in which the impulse reaches and leaves the A-V node. Wenckebach and Winterberg[7] also raise the question whether "the more pronounced disturbances of this type, particularly abnormal intraventricular conduction in APS, are not of more than mere functional significance, and whether they might not indicate disease of the conduction system." Wenckebach, however, answers his own question in the negative, and other authors [Katz,[8] Pardee,[6] and White[3]] do likewise. Carter[5] and Bellet and McMillan,[10] on the other hand, follow Lewis' trend and ascribe definite pathologic significance to the phenomenon of aberration.

Faced with such conflicting statements regarding the significance of aberration in man, we turn to reports on animal experiments, but there, too, we find contradictions. Pardee[6] states that aberrant ventricular complexes are common in normal dogs with artificially induced premature auricular contractions; he considers it difficult to find a reason why there should be a localized abnormality of the auriculoventricular conduction system in normal dogs, even when they are under an anesthetic. Stenstroem,[11] on the other hand, who worked on rabbits, never found the ventricular complexes of artificially produced APS aberrant as long as the hearts were intact. Stenstroem furnished weighty experimental evidence to indicate that aberration is due to impaired conduction through the bundle branches. He invented an apparatus which produces premature systoles by electrical stimulation. Before stimulating the auricles, Stenstroem exerted pressure on those parts of the interventricular septum through which the branches of His' bundle pass, and temporarily injured one of the branches. He waited until the electrocardiogram returned to normal, and then produced APS. These APS showed constant aberration; when the left bundle branch was injured, their ventricular complexes took on the shape of the dextrocardiogram; when the right bundle branch was injured, their ventricular complexes took on the shape of the levocardiogram; and when both bundle branches were injured simultaneously, the ventricular complexes of the APS took on the shape of either the levocardiogram or the dextrocardiogram.

Convincing experimental evidence, such as that of Stenstroem, strengthened us in the belief that, in man, aberration of the ventricular complexes of APS might at times also be indicative of a pathologic condition of the conducting tissues. We decided to investigate the problem in two ways, namely, by electrocardiographic analysis and by correlation of electrocardiographic and clinical observations.

It has often been stated that aberration is usually more marked in those APS which are very premature, and a causal connection between prematurity and aberration has long been assumed. Lewis[1] was the first to note that "the ventricular complex diverges from normal most con-

complex is due, so it is maintained, to defects in conduction through some of the chief Purkinje strands," and he finds it "notable that in these patients minor defects in the main bundle are the rule." On another occasion, Lewis[2] states: "Auricular extrasystoles showing aberrant ventricular complexes are almost confined to hearts in which

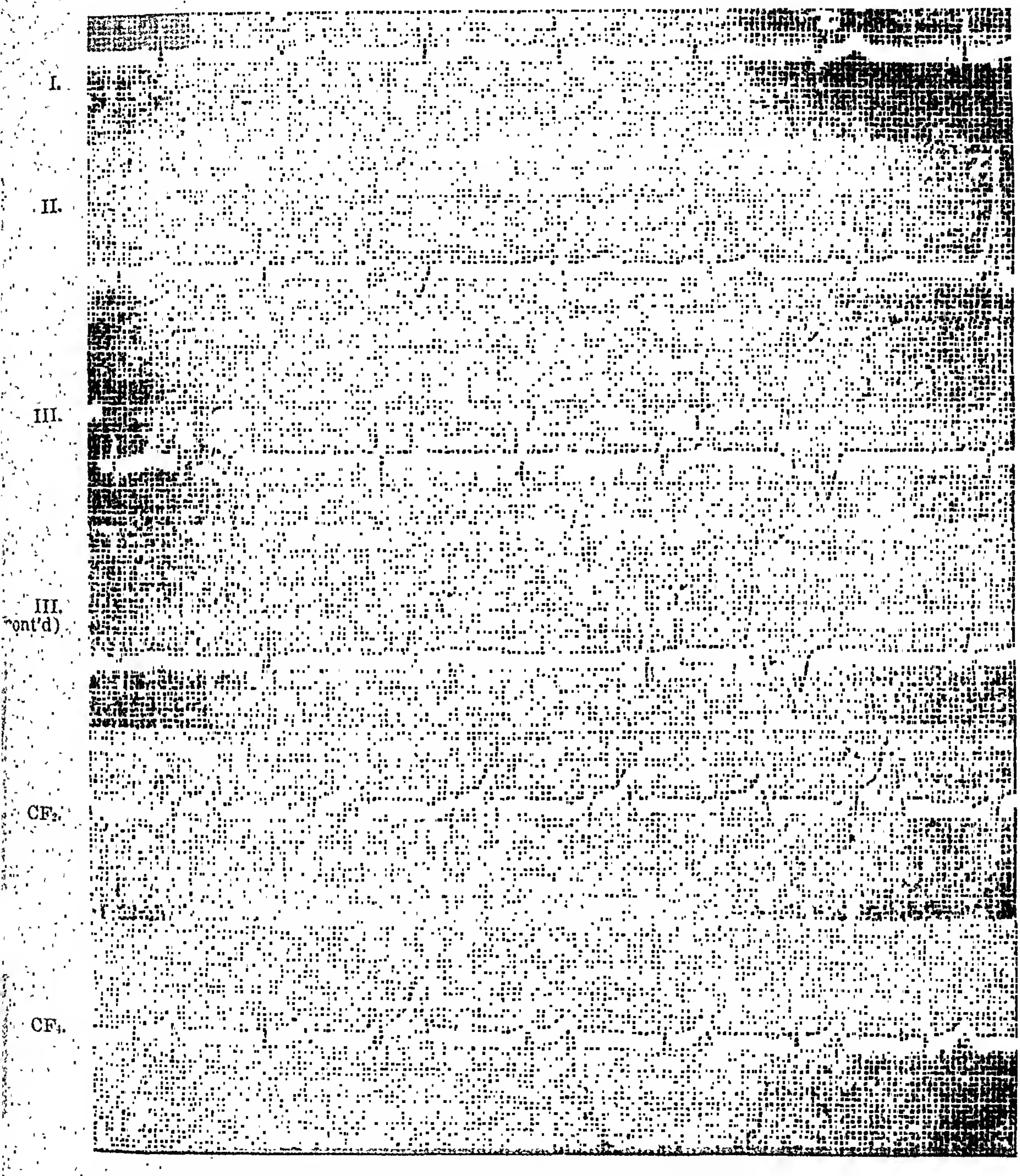


Fig. 10.—Erroneous diagnosis of myocardial damage caused by misinterpretation of an APS. *x*, APS; *y*, blocked APS; *z*, VPS. *x* (in Lead III) is preceded by an inconspicuous P wave which is superimposed on the preceding T wave. The ventricular complex of *x* is bizarre. *x* was, therefore, misinterpreted as a VPS by one examiner. The diagnosis of "myocardial damage" was then based on the finding of "multifocal VPS." Yet apart from the arrhythmia and the notching of P in Lead II, this electrocardiogram is probably within normal limits.

conduction defects in the junctional tissues are demonstrable." Pardee[6] disagrees with Lewis, and finds it hard to believe "that all patients who have premature auricular contractions have either an abnormality of function or structural disease in the A-V conduction system;" he

TABLE IV

INFLUENCE OF PREMATURITY ON ABERRATION

DEGREE OF PREMATURITY	NUMBER OF TYPES	BLOCKED	NO ABERRATION AT ALL	ABERRATION OF T ONLY	QRS CHANGED IN AMPLITUDE ONLY	QRS CHANGED IN DIRECTION ONLY	QRS CHANGED IN DURATION ONLY	QRS CHANGED IN CONFIGURATION ONLY	R TALLER, S SMALLER, OR VICE VERSA	R THE SAME, S DEEPER OR S THE SAME, R TALLER	DIFFERENCE IN SIZE OF Q ONLY	SECOND DEGREE ABERRATION	THIRD DEGREE ABERRATION	FOURTH DEGREE ABERRATION
Late APS (Location I)	101	0	50	15	9	0	2	13	5	1	1	5	0	0
Fairly late APS (Location II)	138	0	33	11	29	0	3	12	16	0	4	20	7	3
Moderately early APS (location III)	180	3	45	10	25	0	2	12	11	1	8	33	18	12
Early APS (Location IV)	100	5	11	5	16	0	3	5	2	0	1	24	17	11
Very early APS (Location V)	6	0	0	0	0	0	0	0	0	0	0	1	3	2
All types	525	8	139	41	79	0	10	42	34	2	14	83	45	28

TABLE V

AURICULAR PREMATURE SYSTOLES (APS) WITH MARKED ABERRATION, AND APS WITHOUT ANY ABERRATION—THEIR LOCATION IN DIASTOLE

	NUMBER OF CASES	NUMBER OF DIFFERENT APS	LOCATION I (LATE IN DIASTOLE)	LOCATION II (FAIRLY LATE IN DIASTOLE)	LOCATION III (MODERATELY EARLY IN DIASTOLE)	LOCATION IV (EARLY IN DIASTOLE)	LOCATION V (VERY EARLY IN DIASTOLE)
Marked (fourth degree) aberration; bizarre ventricular complexes	24	28	0	3	12	11	2
No aberration at all	28	35	20	6	7	2	0

of two or more different degrees of prematurity; there was, therefore, a total of 35 different "types" of APS without any aberration whatever. The majority of these (Table V) occurred late in diastole, and none occurred very early in diastole.

3. We then approached the problem from the opposite side, and grouped our 525 types of APS according to the degree of their prematurity (their location in diastole). The data of this analysis (Table IV) furnish convincing evidence that prematurity influences abberration: none of the 101 APS occurring late in diastole (our "Location I") ever showed the higher degrees of aberration. Conversely, none of the six tyes of APS occurring very early in diastole were free from aberration.

TABLE II

RELATIVE FREQUENCY OF THE DIFFERENT DEGREES OF PREMATURITY OF AURICULAR PREMATURE SYSTOLES (APS)

LATE APS (LOCATION I): THE P WAVE OF THE APS DOES NOT TOUCH THE T WAVE OF THE PRECEDING BEAT	FAIRLY LATE APS (LOCATION II): THE P WAVE OF THE APS BARELY TOUCHES THE DESCENDING LIMB OF THE T WAVE OF THE PRECEDING BEAT	MODERATELY EARLY APS (LOCATION III): THE P WAVE OF THE APS IS SUPERIMPOSED ON THE DESCENDING LIMB OF THE PRECEDING T WAVE	EARLY APS (LOCATION IV): THE P WAVE OF THE APS IS SUPERIMPOSED ON THE ASCENDING LIMB OF THE PRECEDING T WAVE	VERY EARLY APS (LOCATION V): THE P WAVE OF THE APS IS SUPERIMPOSED ON THE PRECEDING RS-T SEGMENT CLOSE TO THE QRS COMPLEX	TOTAL
101	138	180	100	6	525

TABLE III

NUMBER OF DIFFERENT TYPES OF AURICULAR PREMATURE SYSTOLES (APS) PER CASE

NUMBER OF DIFFERENT TYPES OF APS PER CASE	ONE	TWO	THREE	FOUR	FIVE	SIX AND MORE	TOTAL
NUMBER OF CASES	52	51	51	27	11	9	201

spicuously when the extrasystole falls early in diastole; in some patients aberration is closely related to the degree of prematurity." Lewis, who attributes the aberration to deficient conduction along certain tracts of the junctional tissues, explains that "the deficiency has been confined to the premature beats *because the rest preceding these* has been brief."[2] Other authors, namely, Katz,[8] and Scherf and Boyd[9] express the opinion that prematurity is the only cause of aberration. Stenstroem,[11] however, referring to APS in a human subject, reported that "the extent of aberration was *not* entirely determined by the elapse of time between a normal complex and its following extrasystole."

Prematurity and Aberration.—We analyzed our own electrocardiographic material in order to learn whether prematurity was the sole factor determining the degree of aberration. Our results are summarized in Table IV. A number of observations demonstrated the marked influence of prematurity on aberration.

1. We found 24 patients with APS showing "fourth degree" aberration; the abberation affected amplitude, duration, direction, and configuration of the QRS complex, and the APS had a bizarre appearance. Four of the 24 patients exhibited bizarre APS of two different degrees of prematurity; there were, therefore, 28 different "types" of such bizarre APS. None of the 28 occurred late in diastole (Table V). All except two occurred early in diastole, and the two which occurred "fairly late in diastole" (Location II) were associated with slow heart rates (which lengthen diastole).

2. Contrariwise, there were 28 patients with APS which never showed any aberration of either QRS or T. Six of these patients exhibited APS

Were we to judge only by the observations so far mentioned, it might seem that prematurity alone determines the occurrence and the degree of aberration. Other observations of ours, however, do not support that conclusion. In the first place, there were too many exceptions to the rule. Marked prematurity was not necessarily associated with abberation; it actually occurred without it (Table V). There were, for instance, 100 types of early APS (Location IV); 11 of these showed no aberration at all, and five more showed aberration of the T wave or the S-T segment without aberration of QRS (Table IV). In the second place, the many electrocardiograms with several different types of APS in the same record or the same lead showed that different influences were at work; often there was no parallelism between prematurity and aberration. Table VI illustrates this point. In 149 of our 201 cases, multiple types of APS were present, but in only a *small* minority, 16, did aberration increase with increasing prematurity (Fig. 11, *A*); in 12 cases, aberration actually decreased with increasing prematurity (Fig. 11, *B*). The great majority of the 149 cases, however, did not fit in either of these groups. They exhibited three or more different types of APS: in some instances, aberration increased with increasing prematurity in two types, but not in the third; in other instances, other combinations occurred; the various combinations are summarized in Table VI. The entire group of 149 cases of multiple APS included 51 cases with only two types of APS. If we analyze this smaller group alone, we obtain a much clearer picture (Table VII). It is then clear that the degree of prematurity and the degree of aberration are usually not parallel. In only ten of the 51 cases did aberration increase with increasing prematurity; in seven cases it decreased. The remainder of the cases, 34, fell into two groups. In one group, abberation differed even though the degree of prematurity was the same (24 cases) (Fig. 11, *D*); in the other group, prematurity varied while the degree of aberration remained the same (ten cases) (Fig. 11, *C*). From these figures, the lack of a consistent relationship between aberration and prematurity is apparent. We are, therefore, led to the conclusion that prematurity is *not* the sole factor which determines the degree of aberration. In an effort to find other determining factors we then investigated the possible influence of the frequency of the APS and the P-R interval of the APS.

Effect of Frequency of APS on Their Aberration.—Stenstroem[11] reported that the frequency of theAPS influences their aberration. We

TABLE VII

ABERRATION IN THE PRESENCE OF TWO DIFFERENT TYPES OF APS

ABERRATION INCREASES WITH PREMATURITY	ABERRATION DECREASES WITH PREMATURITY	ABERRATION SAME, LOCATION DIFFERENT	LOCATION SAME, ABERRATION DIFFERENT	TOTAL NUMBER OF CASES
10	7	10	24	51

TABLE VI

RELATIONSHIP OF PREMATURITY AND ABERRATION IN 149 CASES SHOWING MULTIPLE TYPES OF APS

ABERRATION INCREASES WITH INCREASING PREMATURITY	ABERRATION DECREASES WITH INCREASING PREMATURITY	SAME DEGREE OF PREMATURITY, BUT DIFFERENT DEGREE OF ABERRATION	SAME ABERRATION, BUT DIFFERENT DEGREE OF PREMATURITY	COMBINATION I: ABERRATION INCREASES WITH INCREASING PREMATURITY IN SOME INSTANCES; SAME DEGREE OF PREMATURITY, DIFFERENT DEGREE OF ABERRATION IN OTHERS	COMBINATION II: ABERRATION DECREASES WITH INCREASING PREMATURITY IN SOME INSTANCES; SAME DEGREE OF PREMATURITY, DIFFERENT DEGREE OF ABERRATION IN OTHERS	TOTAL
16	12	48	11	27	35	149

TABLE VIII

ABERRATION OF AURICULAR PREMATURE SYSTOLES (APS) CORRELATED WITH THEIR FREQUENCY

NUMBER OF APS PER ELECTROCARDIOGRAM	NO ABERRATION AT ALL	MAXIMAL ABERRATION: ABERRATION OF T WAVE ONLY	FIRST DEGREE ABERRATION OF QRS	SECOND DEGREE ABERRATION OF QRS	THIRD DEGREE ABERRATION OF QRS	FOURTH DEGREE ABERRATION OF QRS	TOTAL NUMBER OF CASES
1	14 (48.3%)	0	7 (24.1%)	4 (13.7%)	3 (10.3%)	1 (3.4%)	29
2 to 5	21 (23.1%)	3 (3.3%)	31 (34.1%)	20 (22.0%)	9 (9.9%)	7 (7.7%)	91
6 to 10	6 (13.9%)	1 (2.3%)	10 (23.3%)	16 (37.1%)	4 (9.3%)	6 (13.9%)	43
11 to 20	3 (10.0%)	1 (3.3%)	9 (30.0%)	5 (16.7%)	4 (13.3%)	8 (26.7%)	30
21 to 30	1 (14.3%)	0	1 (14.3%)	2 (28.6%)	1 (14.3%)	2 (28.6%)	7
31 and over	0	0	0	1 (100.0%)	0	0	1
	45	5	58	48	21	24	201

showed a fairly even distribution of the different degrees of aberration, and absence of aberration was about as frequent as "second degree" aberration. The highest degrees of aberration, in general, are infrequent; they, therefore, could not be expected to be numerous in this group. In any event, it should be remembered that the number of cases available for analysis was small, and that the findings were equivocal. We felt justified in concluding that no definite relationship exists between the frequency of APS and the aberration of their ventricular complexes.

P-R Interval and Aberration.—We occasionally encountered two types of APS in the same record which differed greatly in the duration of their P-R intervals, and it occurred to us that the difference in aberration might depend on the difference in the P-R intervals; the APS with a long P-R interval might possibly show marked aberration, and the APS with a short P-R interval might possibly be free from aberration. To investigate the relationship, we again used our two extreme groups, APS without any aberration, and APS with marked aberration. In both groups (Table IX) we found APS with P-R intervals longer than

TABLE IX

P-R INTERVALS OF AURICULAR PREMATURE SYSTOLES (APS) WITHOUT ABERRATION, AND OF APS WITH MARKED ABERRATION

	NUMBER OF CASES	P-R INTERVAL RELATIVELY PROLONGED	P-R INTERVAL RELATIVELY SHORTENED	P-R INTERVAL THE SAME AS THAT OF NORMAL BEATS
APS without aberration	28	8 (29.5%)	12 (41.0%)	8 (29.5%)
APS with marked (fourth degree) aberration	24	13 (52.2%)	8 (34.8%)	3 (13.0%)

grouped our cases according to the total number of APS found in each electrocardiogram, and compared the occurrence of the different degrees of aberration in the different frequency groups (Table VIII). Contrasting only the extremes, we did indeed find a difference between cases with only a single APS and those with 21 or more in one record; half (48.3 per cent) of the APS which occurred singly showed no aberration at all, whereas abberation, especially of the higher degrees, was

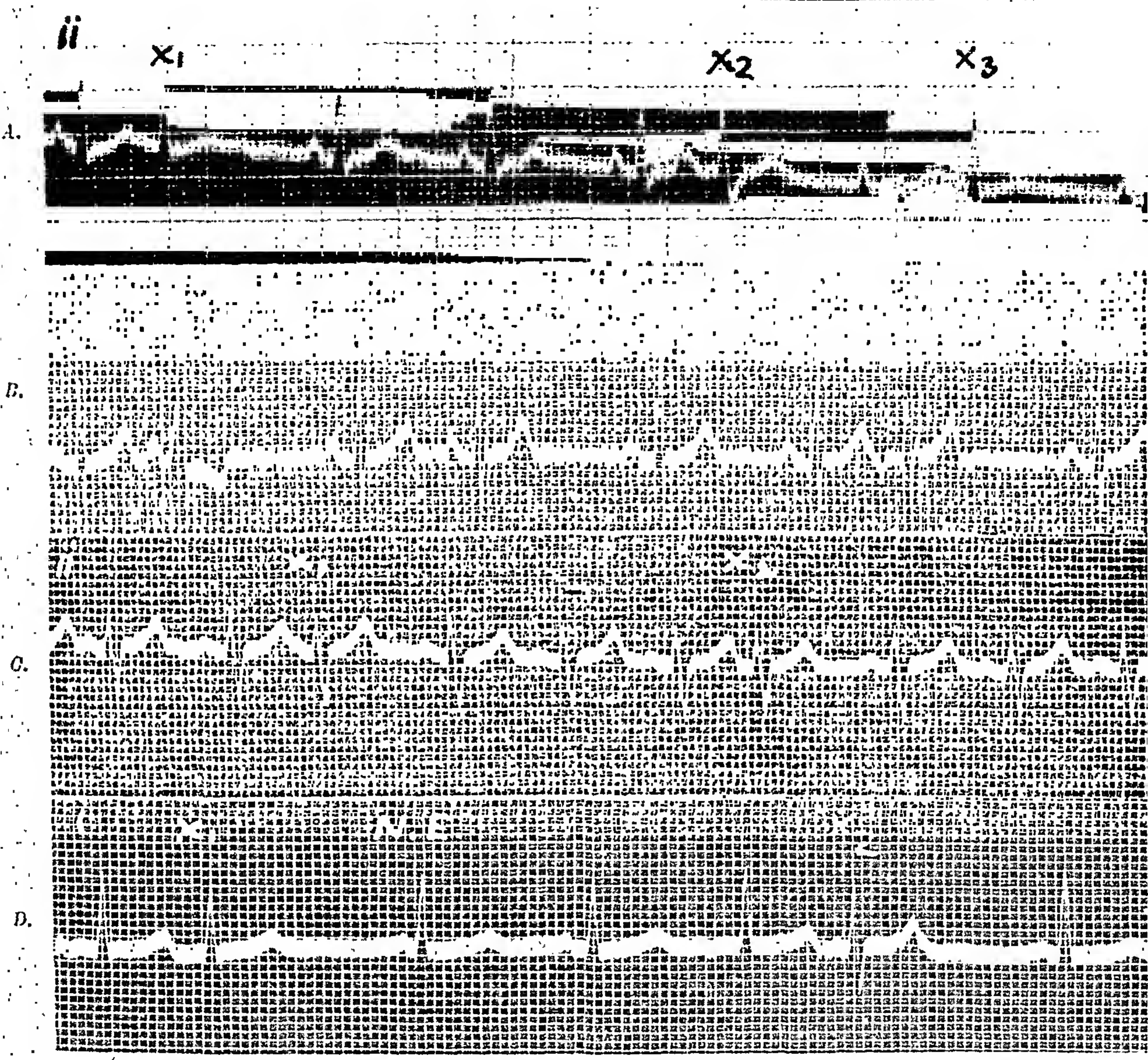


Fig. 11.—Multiple APS, showing the varying relationship between aberration and the degree of prematurity. *A*, Aberration increases with increasing prematurity. x_1 and x_3, APS of Location III, show first degree aberration; x_2, APS of Location IV, shows second degree aberration. *B*, Aberration decreases with increasing prematurity. x_1, APS of Location II, shows third degree aberration; x_3, APS of Location III, shows first degree aberration. *C*, Aberration the same, location varies. x_2 is more premature than x_1, yet shows no more aberration. *D*, Location the same, aberration varies. x_1 and x_2 both have Location III, yet x_2 shows more aberration than x_1.

frequent in records containing a multitude of APS. The relationship, however, became much less definite when records showing a moderate number of APS per tracing were analyzed, and such records were more numerous. Records with two to five APS per tracing, for instance,

TABLE XI

CORRELATION OF AGE AND DEGREE OF ABERRATION

	NO ABERRATION AT ALL	FOURTH DEGREE ABERRATION
Number of cases	28	24
Average age (yrs.)	56½	55

Age Factor.—We studied the age factor first. A pathologic condition of the conduction system, we thought, was more likely to be present in older patients. We first noted the ages of all patients (24) with "fourth degree aberration," and then, by way of contrast, the ages of all patients (28) whose APS showed no aberration at all (Table XI). In the latter group, the average age was 56½ years, and, in the former, it was 55 years; the difference was obviously insignificant. We then grouped all our patients according to age, and found that marked aberration was no more frequent among the aged than among the young. We also observed marked aberration in children. Conversely, we found APS without any aberration in the electrocardiograms of several patients over 70 years of age. Our analysis of the age distribution, therefore, failed to give us a clue to the "missing factor."

Aberration in Cardiac and Noncardiac Patients.—We divided our patients into three groups, according to diagnosis: 29 noncardiac patients, 103 cardiac patients without congestive heart failure, and 63 cardiac patients with congestive heart failure (Table XII). Six cases were ex-

TABLE XII

CORRELATION OF CARDIAC STATUS AND DEGREE OF ABERRATION

	NONCARDIAC PATIENTS	CARDIAC PATIENTS WITHOUT SIGNS OF CONGESTIVE HEART FAILURE	CARDIAC PATIENTS WITH CONGESTIVE HEART FAILURE	EXCLUDED FROM ANALYSIS BECAUSE OF INADEQUATE DIAGNOSTIC STUDY
NUMBER OF CASES	29	103	63	6
ABERRATION VARIED FROM	None to fourth degree aberration	None to fourth degree aberration	None to fourth degree aberration	None to second degree aberration
NUMBER OF CASES IN WHICH NO ABERRATION OCCURRED	4	15	7	2
NUMBER OF CASES IN WHICH FOURTH DEGREE ABERRATION OCCURRED	2	15	7	0
PREMATURITY VARIED FROM	Location I to Location V	Location I to Location IV	Location I to Location V	Location I to Location IV

those of the normal beats, and APS with shorter P-R intervals. There were more instances of relative P-R interval prolongation among APS with marked aberration than among those without aberration. The preponderance, however, was not striking; probably it was incidental and due to greater frequency of A-V conduction disturbances in this group. Negative results were also obtained when we approached the problem from the opposite side. We collected all APS with abnormally prolonged P-R intervals and all APS with very short P-R intervals, and compared the incidence of aberration in both groups; there was no significant difference (Table X). We concluded, therefore, that P-R interval changes in APS have no demonstrable influence on the aberration of their ventricular complexes.

TABLE X

OCCURRENCE OF ABERRATION IN AURICULAR PREMATURE SYSTOLES (APS) WITH PROLONGED P-R INTERVALS AND APS WITH SHORT P-R INTERVALS

	NUMBER OF CASES	NO ABERRATION	FIRST DEGREE ABERRATION	SECOND DEGREE ABERRATION	THIRD DEGREE ABERRATION	FOURTH DEGREE ABERRATION
APS with abnormally prolonged P-R intervals	12	7	2	0	0	3
APS with short P-R intervals	20	8	8	4	0	0

Correlation of Clinical and Electrocardiographic Observations.—The electrocardiographic part of our investigation was thus concluded. It had shown that the degree of prematurity of APS had an influence on the aberration of their ventricular complexes, but that it was not the only determining factor. Our results had strongly suggested that other factors might be operative. The clinical part of our study was essentially a search for these other factors. Our aim was to investigate the influence of pathologic conditions on aberration. In this effort, we were encouraged by Stenstroem's[11] experiments on rabbits, previously described, for we regarded it as probable that Stenstroem's conclusions applied to human hearts as well.

In our clinical study, we analyzed the charts of the 201 patients and, in each case, carefully noted the diagnosis, as well as the significant findings on which it was based. A large number of the patients were examined by us personally. In cardiac patients, special note was made of the presence or absence of congestive heart failure and its objective signs. When changes in the cardiac status occurred, they were noted. Whenever a patient received a drug known to affect the electrocardiogram, for instance, digitalis or quinidine, the fact was recorded. Note was also made of the patient's age, blood pressure, and all roentgenologic and laboratory data.

failure nor other features of the cardiac status had any influence on aberration.* It may be argued that the number of patients in each group was too small, that diagnostic errors could not always be tracked down, and that necropsy findings were available in very few cases. We doubt whether our results would have been different, had the number of patients and necropsies been greater. We believe that our conclusion is valid because our analysis did not give the slightest hint of a relationship between cardiac status and aberration.

Change of Aberration in Serial Electrocardiograms.—Our results, so far, had been uniformly negative, but we approached the problem from still another angle, and this approach proved more successful. We studied serial electrocardiograms of patients who repeatedly exhibited APS, and searched these records for variations in the degree of aberration. As a rule, the configuration of APS did not change, even over long periods, provided they arose in the same focus and the degree of their prematurity was the same. In certain instances, however, the degree of aberration did change, and these were the records we used for correlation. We compared the clinical condition of these patients at the time of their first electrocardiogram with the condition at the time of subsequent tracings, and found that the change in aberration corresponded to a change in the clinical condition. This observation, for the first time, suggested that aberration is a finding of clinical significance. To illustrate this point, three characteristic cases will now be reported.

CASE REPORTS

CASE 1.—F. K., aged 31 years, admission No. 21241, was admitted to the hospital March 14, 1932, with the typical signs of lobar pneumonia in the left lower lobe. On March 15, 1932, the patient was profoundly toxic; the temperature was 105° F., and the leucocyte count was 42,500. The electrocardiogram taken on that day showed evidence of myocardial impairment (low amplitude of the T waves in Lead II). Numerous APS were present, and their QRS-T complexes, especially in Lead III (Fig. 12, *A*) showed aberration (lower amplitude of QRS, duration of QRS, decreased from 0.08 to 0.07 second, notching of the R wave near its tip, absence of the S wave, elevation of the RS-T junction, and increased inversion of the T wave). On April 6, 1932, when the patient had been afebrile and convalescent for twelve days, a second electrocardiogram was taken (Fig. 12, *B*). It showed no more evidence of myocardial damage (the T waves in Lead II were now of normal amplitude). The APS of this electrocardiogram, which arose in the same focus as those of March 15, 1932, showed only minimal aberration of the QRS complexes (lower amplitude of R, slightly decreased duration of QRS) and very little aberration of the T waves. The change from marked to minimal aberration in this case was quite remarkable. No drugs known to affect the electrocardiogram had been given to the patient. We are inclined, there-

*In this connection another observation may be mentioned. The APS of the noncardiac patients showed all degrees of prematurity. They did not differ from those of the two cardiac groups in that respect, either.

TABLE XIII

AURICULAR PREMATURE SYSTOLES (APS) IN NONCARDIAC PATIENTS

CASE	AGE (YRS.)	DIAGNOSIS	DEGREE OF PREMATURITY	MAXIMUM DEGREE OF ABERRATION
1	12	Lobar pneumonia	Locations I & II	First degree
2	45	Lobar pneumonia	Locations IV & V	Third degree
3	34	Lymphogranuloma venereum	Location I	Aberration of T only
4	28	Infectious arthritis	Location IV	Second degree
5	39	Subdeltoid bursitis	Location I	First degree
6	42	Cystocele	Locations II & III	Second degree
7	17	Psychoneurosis	Location II	First degree
8	23	Pulmonary embolization following cesarean section	Location IV	Blocked APS
9	34	Cholecystitis	Location III	First degree
10	14	Tonsillitis	Location II	No aberration
11	12	Bronchopneumonia	Location III	Fourth degree
12	58	Pernicious anemia	Location II	First degree
13	70	Carcinoma of lung	Location IV	First degree
14	9	Cervical lymphadenitis	Location I	First degree
15	31	Lobar pneumonia	Location II	First degree
16	48	Fracture of skull	Location II	Second degree
17	58	Bronchopneumonia	Locations III & IV	First degree
18	38	Bronchial asthma	Location II	Second degree
19	2	Lobar pneumonia	Location I	No aberration
20	19	Bronchial asthma	Location II	Third degree
21	36	Gonorrheal arthritis	Location III	Third degree
22	21	Healthy adult	Location III	First degree
23	27	Cellulitis of face	Location III	Second degree
24	53	Healthy adult	Location I	No aberration
25	53	Bronchial asthma	Location IV	Fourth degree
26	44	Tuberculous lymphadenitis	Location IV	Blocked APS
27	79	Adenocarcinoma of colon	Location IV	Second degree
28	48	Hodgkin's disease	Location III	First degree
29	23	Thrombosis of cerebral artery	Location I	No aberration

cluded because of inadequate diagnostic study. We then attempted to correlate the cardiac status of the patients with the degree of aberration. The results were disappointing; there was little difference among the three groups. In the noncardiac group (Table XIII), all degrees of aberration occurred, including "fourth degree aberration" with bizarre ventricular complexes (two cases). Absence of aberration occurred only four times. The distribution was not significantly different from that in the two cardiac groups. In these also, all degrees of aberration occurred, and, remarkably enough, complete absence of aberration was found quite frequently, i.e., fifteen times among the 103 cardiac patients without congestive heart failure, and seven times among the 63 cardiac patients with congestive heart failure. Several patients of the last group were very ill; some were suffering from acute myocardial infarction, and others, from pulmonary infarction, but their electrocardiograms otherwise thoroughly abnormal, showed APS without aberration. The electrocardiogram of a moribund patient which showed left bundle branch block also showed APS without any aberration. Absence of aberration was common in normal and abnormal electrocardiograms alike. Our conclusion was that neither the presence nor the absence of heart

necropsy was not obtained. The two electrocardiograms were taken at an interval of only two days, yet the difference in aberration was striking. Two explanations for this difference seem possible. On the day before the patient's death, her myocardium may have deteriorated, and a pathologic condition of the conduction system may have developed which manifested itself in increased aberration of the APS; or quinidine may have affected the conduction system. The second explanation seems more plausible in view of the other evidence of quinidine effect (prolongation of Q-T), and in view of the facts learned from the next case.

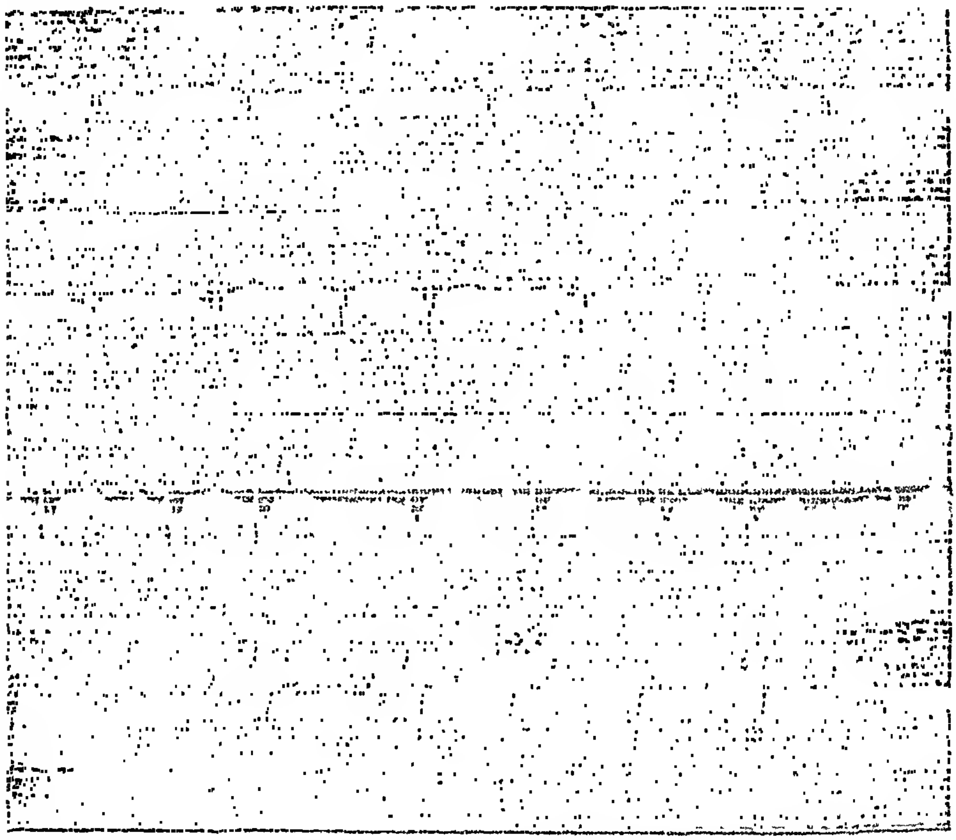


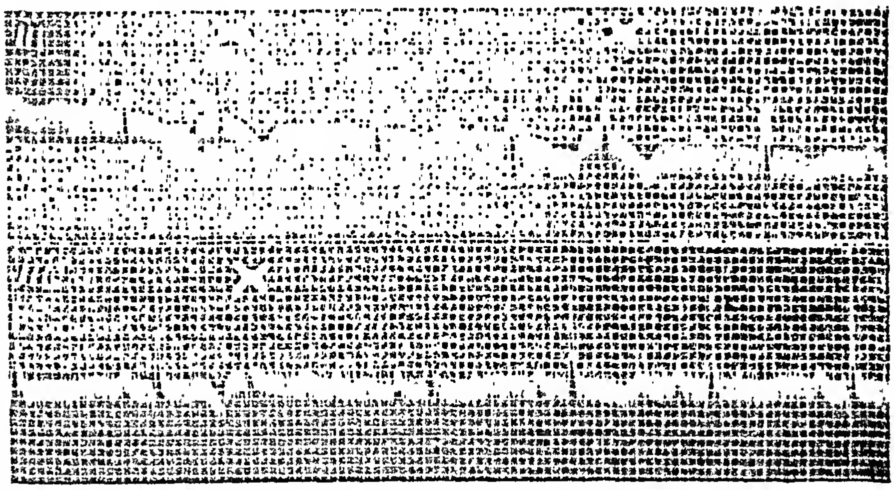
Fig. 13.—Case 2. Marked increase in aberration of APS after quinidine administration in a case of fatal atypical myocardial infarction. Record taken Dec. 21, 1941, reveals numerous APS (x_1, x_2, and x_3), with no aberration of QRS and minimal aberration of the T waves.

CASE 3.—A. H., admission No. 63394, a 73-year-old man, was admitted to the Cardiac Clinic suffering from essential hypertension (blood pressure 180/100). He had no complaints referable to the heart, but presented a cardiac irregularity which, as the electrocardiogram (Fig. 15) showed, was caused by numerous APS. These APS exhibited varying degrees of aberration which did not depend on the degree of prematurity. A few beats, e. g., x_2 in the third lead, showed aberration affecting amplitude, configuration, and direction of the QRS complexes, and also an increase in the size of the T wave; other APS, on the other hand, especially those occurring a little later in diastole (x_1 in the second lead), showed only minimal aberration of QRS-T. The tracings were otherwise within normal limits for a patient of that age, with one possible exception: the low amplitude of the R wave in Lead CF_2.

fore, to ascribe the decrease in aberration to the improvement of the clinical condition. It seems very probable to us that the severe pneumonia had been a cause of the aberration.

CASE 2.—S. R., aged 70 years, admission No. 70366, a case of hypertensive heart disease of at least ten years' duration, was admitted to the hospital Dec. 4, 1941, acutely ill with pneumonia in the left lower lobe. On admission, premature beats were heard, but no electrocardiogram was taken. The pneumonic process responded promptly to treatment with sulfadiazine, and the temperature, which had been 101.8° F., became normal within three days. On Dec. 20, 1941, the patient's convalescence was interrupted by an attack of acute left ventricular failure which was assumed to be secondary to myocardial infarction; her temperature, on that day, rose to 103° F. An electrocardiogram taken the following day (Fig. 13) showed numerous APS and evidence of myocardial damage (low voltage and slurring of the QRS complexes in the standard leads, with a broad Q wave in Lead I, depression of the RS-T segment in Leads I and IVF, diphasic T waves in Leads I and IVF, and low amplitude of the T waves in Lead II). The patient then received 1.8 Gm. of quinidine sulfate within two days. On Dec. 23, 1941, she suffered a left-sided hemiparesis, presumably due to a

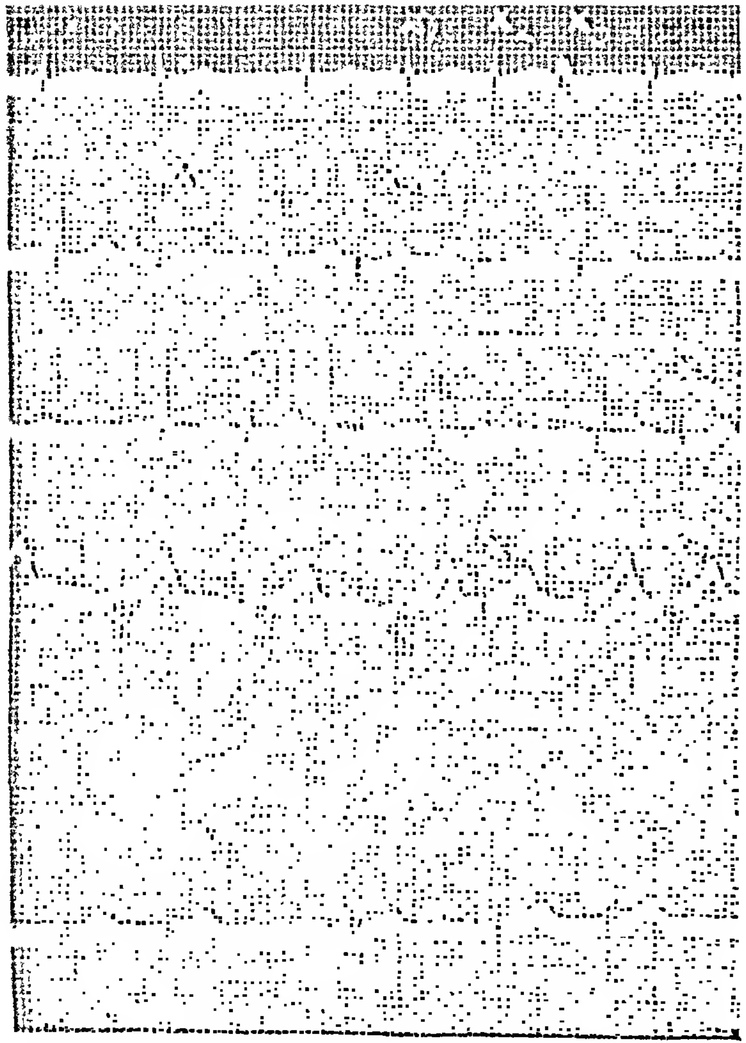
A.



B.

Fig. 12.—Case 1. Change in aberration during the course of severe pneumonia. *A*, Record taken March 15, 1932 (only Lead III is shown) shows two APS (*x*, *x*), with fairly marked aberration (QRS of lower amplitude, QRS duration decreased from 0.08 to 0.07 second, notching of the R wave near its tip, absence of the S wave, elevation of the RS-T junction, increased inversion of the T wave). The patient, on that day, was profoundly toxic, with a temperature of 105°F. and a leucocyte count of 42,500. *B*, Record taken April 6, 1932 (only Lead III is shown) shows one APS (*x*) with slight aberration (QRS of lower amplitude, slight elevation of RS-T junction). The patient, on that day, was afebrile and convalescing.

cerebral embolus; her cardiac condition remained grave. A second electrocardiogram was taken on that day (Fig. 14); it differed from the first in several points: higher amplitude of T_2 and T_3, prolongation of the Q-T interval from 0.35 second to 0.42 second, and, what is of greatest interest here, a higher degree of aberration of the APS. In the earlier tracings, the APS showed no aberration of QRS and minimal aberration of the T waves. In the second record, however, the APS showed QRS complexes which differed from those of the normal beats in three features (change in amplitude, best seen in Lead III, change in duration, best seen in Lead II, and change in configuration, best seen in Lead IVF). The patient died Dec. 24, 1941; permission for



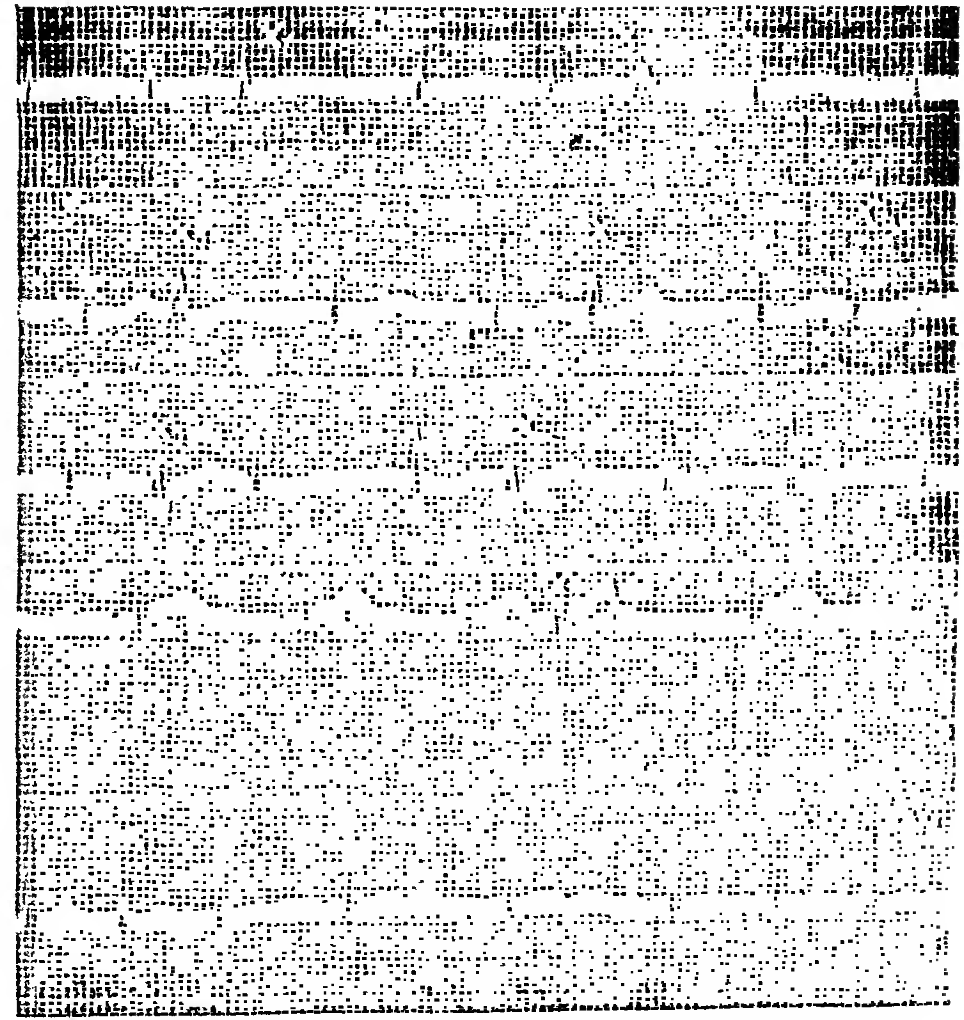


Fig. 15.—Case 3. Marked increase in aberration of APS after quinidine administration in a case of essential hypertension. Record taken March 22, 1914, reveals numerous APS (x_1, x_2, and x_3) with varying degrees of aberration.

Fig. 16.—Case 3. Marked increase in aberration of APS after quinidine administration in a case of essential hypertension. Record taken March 29, 1914, again shows numerous APS (x_1, x_2, and x_3). There is now a marked increase in aberration. x_2 in Lead I shows marked increase in duration of QRS as compared to x_1 in Lead I of Fig. 15. x_1 and x_2 in Lead II show increase in duration and change in configuration of QRS as compared to x_1 and x_2 of Lead II in Fig. 15. x_1 and x_2 in Lead III show marked increase in duration and change in configuration of QRS as compared to x_2 in Lead III of Fig. 15.

In the interval between these two records, the patient had received 6.3 Gm. of quinidine sulfate.

The patient was then given 0.3 Gm. of quinidine sulfate three times a day, by mouth, for one week, during which time his condition did not change in any way. Another electrocardiogram was taken at the end of that week (Fig. 16). The normal beats of the second record showed only slight changes from those of the first (lower amplitude of the T waves in all leads, and prolongation of the Q-T interval from the original 0.37 second to 0.42 second, measured in Lead CF_2). The APS of the second record, however, were for the most part markedly different. A few still showed little aberration, e. g., x_3 in Lead II,

I.

II.

III.

IVF.

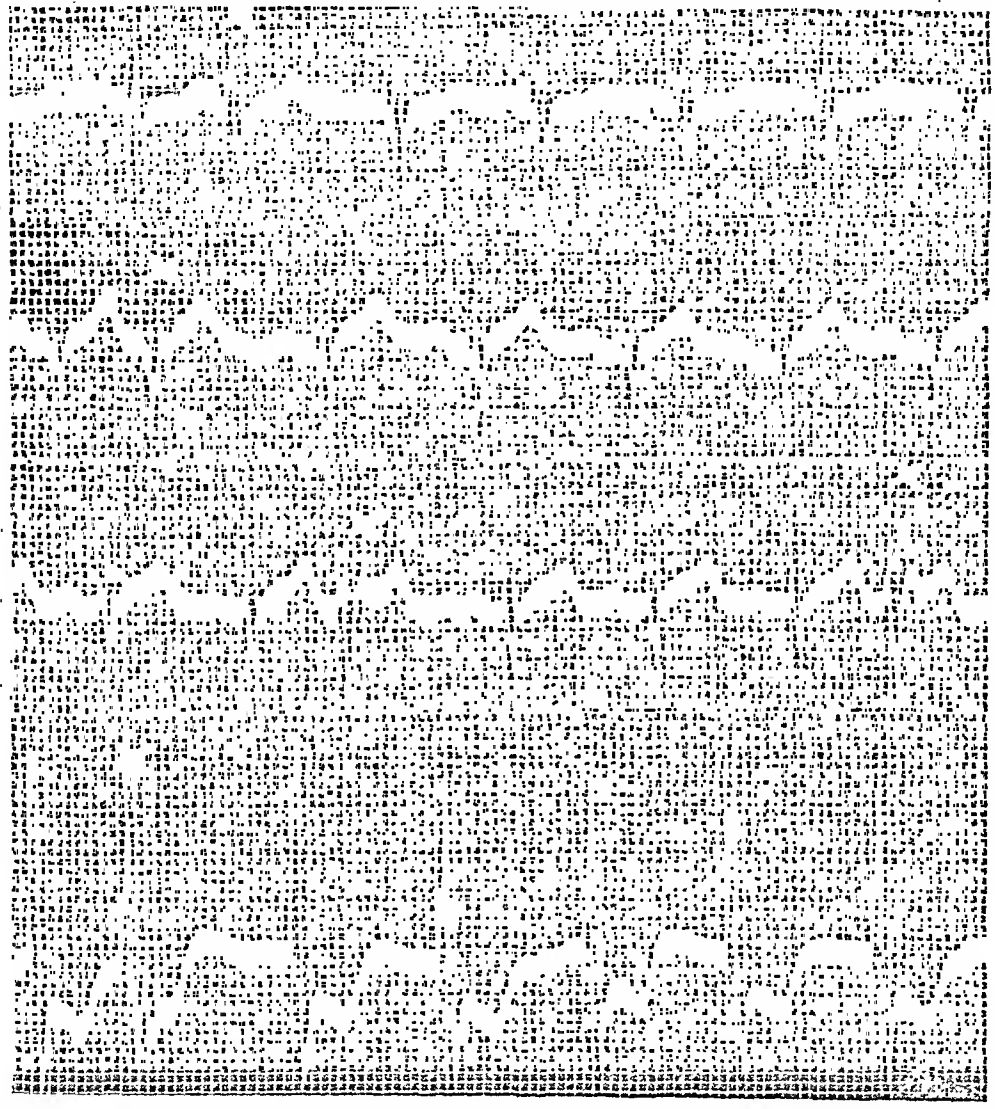


Fig. 14.—Case 2. Marked increase in aberration of APS after quinidine administration in a case of fatal atypical myocardial infarction. Record taken Dec. 23, 1941, shows APS (x, x_1, and x_2) with fairly marked aberration [increase in amplitude of QRS (Lead III), change in duration of QRS (Lead II), change in configuration of QRS (Lead IVF), elevation of RS-T junction (Lead III), increase in amplitude of the T waves (Lead I)].

In the interval between these two records, the patient had received 1.8 Gm. of quinidine sulfate. She died Dec. 24, 1941.

but the majority showed marked aberration. The duration of the QRS complex particularly was affected; it was increased to 0.13 second from a previous maximum of 0.10 second (x_2 in Lead I and x_1 in Lead II). (Incidentally, several APS showing much aberration were *not* more premature than others showing little aberration.) The increase in aberration which had occurred within one week was most

SUMMARY

1. The electrocardiograms of 201 patients who had auricular premature systoles (APS) were analyzed. One thousand three hundred six APS were found, and were divided into five groups according to the degree of their prematurity. Multiple APS of the same degree of prematurity occurring in one record were counted as one "type." Multiple APS of different degrees of prematurity were counted as different "types." The total number of "types" of APS was 525. Eight of these were blocked.

2. APS with aberration of the ventricular complexes were three times as frequent as APS without aberration.

3. If no aberration is present, the APS may be overlooked, or the irregularity may be misinterpreted as sinus arrhythmia.

4. Aberration, especially of the T wave, is often more marked in the chest leads. Chest leads may thus aid in the recognition of APS.

5. Forty-three types showed no aberration of QRS, but showed aberration of the RS-T segments or the T waves.

6. Three hundred thirty-seven types of APS showed aberration of the QRS complexes.

7. If aberration of QRS was of slight degree, increase or decrease in amplitude was the most frequent single change; changes in configuration (slurring, notching, appearance of a Q wave) were next in frequency; changes in duration occurred seldom except in conjunction with other changes; a reversal of direction never occurred alone.

8. The higher degrees of aberration were less frequent than the lower. They consisted of changes in amplitude combined with changes in configuration, or various combinations of changes in amplitude, configuration, duration, and direction.

9. The highest degree of aberration (twenty-eight types) affected all four characteristics of the QRS complex, amplitude, configuration, duration, *and* direction. APS with such bizarre ventricular complexes are commonly mistaken for ventricular premature systoles.

10. The degree of prematurity of an APS is a major factor in determining the degree of its aberration. This was shown by the following facts:

a. None of the twenty-eight types of APS with very marked aberration occurred late in diastole.

b. None of the thirty-five types of APS without any aberration occurred very early in diastole.

c. None of the 101 types of APS occurring late in diastole showed more than moderate aberration.

d. None of the six types of APS occurring *very* early in diastole were free from aberration.

striking. In the absence of any clinical change, there could be little doubt that it was the result of quinidine administration.

This case, we believe, sheds a good deal of light on the problem of aberration. Quinidine is a drug known to slow intraventricular conduction. In this instance, it had little effect on the intraventricular conduction time of the normal beats, but it selectively affected the intraventricular conduction time of the APS.* The cause of this selective action is not known, but it may well lie in the prematurity of the APS. The APS occurred so early in diastole that the conducting tissues had not yet fully recovered from their activity during the preceding normal beat, and their state of incomplete recovery might have made them more vulnerable to the action of quinidine.

The three cases just reported were selected from a much larger number of patients who had serial records. In many of these, multiple APS were present, and aberration varied a great deal within one lead; it would have been difficult to compare these records with subsequent ones. Such electrocardiograms were obviously unsuitable for correlation with clinical observations. Other cases had to be eliminated for a different reason. After the administration of quinidine, the electrocardiograms frequently showed no more APS at all; they had been abolished by quinidine. Our total number of suitable serial records is, therefore, too small for statistical analysis, yet we believe that the three cases reported here, together with the facts previously presented, may serve as a basis for the following conclusions.

CONCLUSIONS

Aberration of the ventricular complexes of APS reflects changes in the intraventricular conduction system. These changes may be physiologic, e.g., if the APS occur very early in diastole; or they may be pathologic. In the latter case, they may be brought about by diseases or by drugs affecting intraventricular conduction, of which quinidine is an example. More important than aberration itself is a change in the degree of aberration. Such a change is always a significant electrocardiographic findings. It indicates a change in the condition of the patient's heart which the remainder of the electrocardiogram may not clearly show. In two of our cases, the change was probably brought about by the administration of quinidine, and, in the third, by a severe infection (pneumonia). Other factors will probably come to light once the subject of aberration receives more attention. Serial records of patients with APS are especially worthy of study. If changes in the clinical condition of such patients occur, serial records should be analyzed for possible changes in the degree of aberration. For the same reason, serial records should be taken of patients with APS if they receive quinidine or other drugs known to affect the electrocardiogram.

*A pathologic condition likewise can affect the configuration of premature systoles selectively, as was recently demonstrated by Dressler[12] in a case of acute myocardial infarction masked by bundle branch block. In Dressler's case, the electrocardiographic changes indicative of infarction were absent in the normal beats, but were displayed by *ventricular* premature systoles.

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11. The degree of prematurity is not the only factor which determines the degree of aberration. This was shown by the following facts:

a. Of one hundred types of APS occurring early in diastole, eleven showed no aberration.

b. Most electrocardiograms showing different types of APS in the same record revealed a lack of parallelism between aberration and the degree of prematurity; aberration often remained the same or became less marked as the degree of prematurity increased.

12. No definite relationship was found to exist between the number of APS in a given record and the aberration of their ventricular complexes.

13. P-R interval changes in APS had no influence on the aberration of their ventricular complexes.

14. The patient's age had no influence on aberration. APS with marked aberration were found in children. APS without any aberration were found in patients over 70 years of age.

15. Aberration occurred in normal and abnormal electrocardiograms. Aberration of all degrees occurred in noncardiac patients as frequently as in cardiac patients. Aberration was no more frequent in the presence of congestive heart failure than in its absence.

16. Three cases are reported. Their serial records showed that significant changes in the degree of aberration of the APS occurred within a few days. In two cases, the change was probably brought about by the administration of quinidine, and, in the third, by a severe infection (pneumonia).

17. Aberration of the ventricular complexes of APS reflects changes in intraventricular conduction; these changes may be physiologic; or they may be pathologic and may then be produced by diseases or by drugs affecting the conduction system, e. g., quinidine.

18. Quinidine selectively affects APS by increasing their aberration, especially the duration of QRS.

19. A change in the degree of aberration is more significant than aberration itself. It indicates a change in the condition of the heart which the remainder of the electrocardiogram may not clearly reveal.

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The third theory, also referred to as the bundle of Kent theory, has been most widely accepted. The experimental work of Butterworth and Poindexter[6] offers some evidence in favor of this theory.

The purpose of this report is not to add another case of Wolff-Parkinson-White syndrome to the literature, but to present some unusual features of this syndrome in the case to be described.

REPORT OF CASE

A 31-year-old soldier was admitted to the Station Hospital at Camp Hale, Colorado, Dec. 14, 1943, for rheumatic fever with cardiac involvement. In addition, he gave a history very suggestive of attacks of paroxysmal tachycardia during the preceding five years, one of which he had the day before admission.

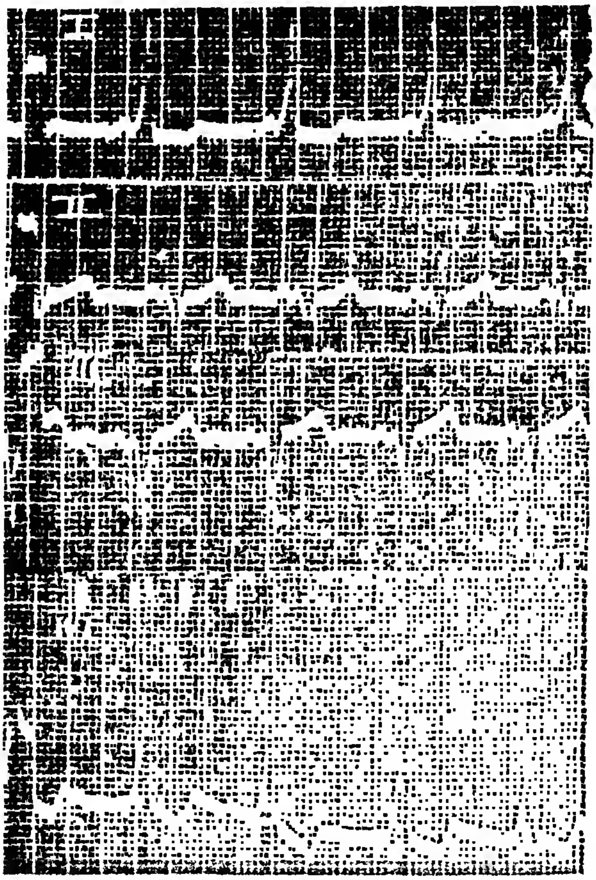

Fig. 1.—Dec. 14, 1943; Wolff-Parkinson-White syndrome.

The electrocardiogram on the day of admission showed the characteristic pattern of the Wolff-Parkinson-White syndrome, i.e., a short P-R interval with a prolonged, aberrant QRS complex of the bundle branch block type (Fig. 1).

During the latter part of his convalescence in the hospital, on April 15, 1944, the patient suddenly had an attack of cardiac palpitation; this was the same complaint which he has had for five years, and, on examination, his cardiac rate was found to be 190 per minute. The electrocardiogram at this time showed paroxysmal nodal tachycardia,

WOLFF-PARKINSON-WHITE SYNDROME WITH UNUSUAL FEATURES

CAPTAIN M. H. STEIN, M.C., ARMY OF THE UNITED STATES

THE electrocardiographic pattern of a short P-R interval associated with a QRS complex of the bundle branch block type has been described many times. In 1915, Wilson[1] described a case in which he believed that vagal stimulation produced an electrocardiogram with a short P-R and bundle branch block type of QRS, and that this was due to A-V nodal rhythm. In 1937, Bishop[2] reviewed the literature and found that forty-five cases had been reported. The first complete report of this condition was made in 1930 by Wolff, Parkinson, and White.[3]

This condition may be more frequent than is evident from the literature, inasmuch as not all cases are being reported. Wolferth and Wood[4] state that, in about a thousand electrocardiograms, one case may be encountered in which an abnormally short P-R interval is associated with a widened QRS complex, and that the latter is markedly aberrant in its initial portion. In a series of 933 patients who had electrocardiograms at this station hospital in the past year, this electrocardiographic pattern was found three times.

All authors agree that this syndrome, per se, is not indicative of organic heart disease. In the series of eleven cases reported by Wolff, Parkinson, and White[3] there were only two cases in which there was evidence of organic heart disease. In Wolferth and Wood's[4] series of nine cases, there were also two patients with organic heart disease. The majority of these patients give a history of attacks of paroxysmal tachycardia of many years' duration.

In the three cases encountered at this hospital there was no evidence of organic heart disease in two, whereas, in the third, which is described in detail below, there was evidence of active rheumatic fever and rheumatic heart disease. Furthermore, this patient with rheumatic fever was the only one who gave a history of paroxysmal tachycardia; he had had it for five years prior to admission. One of the patients had no previous history of any consequence, but the second gave a history of recurrent premature contractions for many years.

Three theories have been suggested as an explanation for the syndrome:[5]

1. It is nodal rhythm or tachycardia, with aberrant conduction in the ventricle.
2. It is regular sinus rhythm, with functional intraventricular block.
3. It is regular sinus rhythm, with a shorter aberrant pathway between the sinoauricular node and ventricular musculature.

Received for publication July 3, 1944.

with a rate of 170 per minute (Fig. 2). The aberrant QRS complexes were replaced by normal ones, as is characteristic of the Wolff-Parkinson-White syndrome during paroxysmal tachycardia.

This tachycardia was stopped by the Valsalva experiment, after the various other methods, usually employed, had failed. Another tracing, taken immediately after the cessation of the attack, showed an unusual feature of the Wolff-Parkinson-White syndrome, i.e., alternation of normal P-R intervals and normal QRS complexes with short P-R intervals and widened, aberrant QRS complexes (Fig. 3). Earlier during his stay in the hospital the patient had developed sinus tachycardia with a rate of 120 per minute and with a return of normal P-R intervals and normal QRS complexes; this was proved electrocardiographically. After the conclusion of this attack, also, a tracing showed the same alternation of normal and aberrant complexes as in Fig. 3.

Subsequent electrocardiograms, taken April 22, 1944, one week after the tracings shown in Figs. 2 and 3, again showed the characteristic Wolff-Parkinson-White syndrome, as Fig. 1.

COMMENT

The interesting electrocardiographic anomaly of a prolonged QRS complex with a short P-R interval, which usually occurs in healthy young persons, was encountered in this case of rheumatic fever. However, since this patient gave the usual history of paroxysmal tachycardia, in this case, for five years, one is inclined to regard the rheumatic fever and the electrocardiographic anomaly as coincidental.

The interesting feature in this case was the alternation of regular and aberrant beats after an attack of sinus tachycardia and also after an attack of paroxysmal nodal tachycardia.

Such alternation is no doubt an unusual occurrence in this syndrome, and perhaps lends weight to the theory that a shorter pathway, the bundle of Kent, does exist, and that the impulses travelled alternately along the bundle of Kent and the bundle of His to produce such an electrocardiographic picture.

CONCLUSIONS

1. In a series of 933 patients who had electrocardiograms, the Wolff-Parkinson-White syndrome was found three times.

2. The patient described in this report was admitted to the hospital because of acute rheumatic fever, but, in addition, had a history of recurrent paroxysmal tachycardia for the preceding five years.

3. The rheumatic fever and the short P-R, prolonged QRS syndrome were probably only coincidental.

4. The unusual phenomenon of normal P-R intervals and normal QRS complexes alternating with the short P-R intervals and aberrant QRS complexes of the so-called Wolff-Parkinson-White syndrome was observed in this case.

The author wishes to express his appreciation and thanks to Captain R. L. Smith for valuable guidance and help in this study.

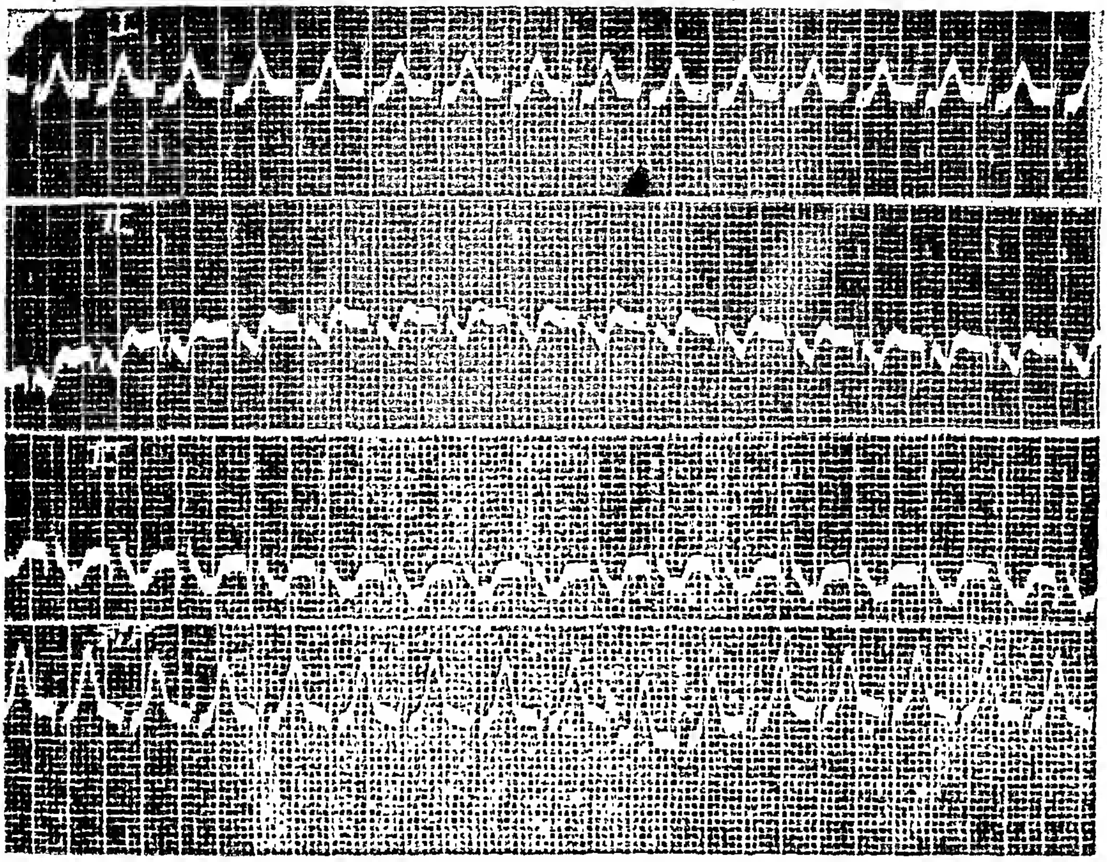

Fig. 2.—April 15, 1944; Paroxysmal A-V nodal tachycardia with disappearance of the complexes of the Wolff-Parkinson-White syndrome.

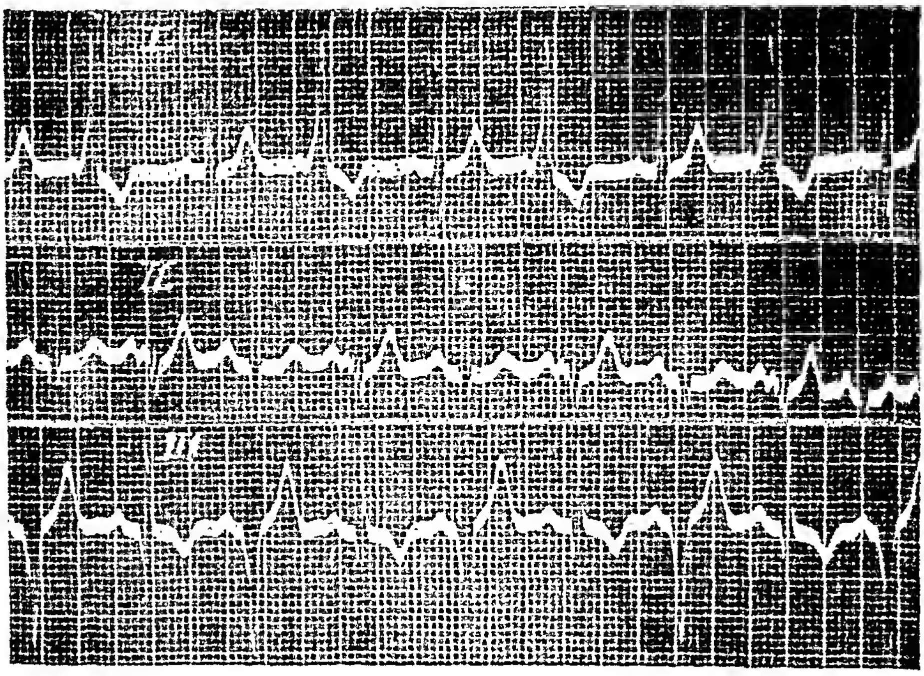

Fig. 3.—April 15, 1944; Normal P-R intervals and QRS complexes alternating with those of Wolff-Parkinson-White syndrome immediately after cessation of attack of paroxysmal nodal tachycardia.

COMPARISON OF THE THERAPEUTIC EFFECTIVENESS OF SERUM AND SODIUM CHLORIDE IN SCALD SHOCK

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As a result of the present war, burns and shock following burns have assumed increasing importance because of their high frequency among members of our Armed Forces and also among the civilian population. As yet, there is a marked difference of opinion regarding the treatment of these conditions. It is the purpose of the group of experiments presented here to ascertain more effective methods for the treatment of shock.

One of the chief aspects of the treatment of burn shock, as well as other types of traumatic shock, is the administration of fluid to help restore the lowered blood volume to normal. The solutions which have been used to replace vascular fluid loss are numerous, and include normal saline, glucose or glucose-saline solutions, saline solutions containing colloids such as serum albumin, gum acacia, or gelatin, blood serum or plasma, and whole blood. Because the vascular fluid lost in burns is essentially plasma, treatment with plasma or serum has appeared to be most logical, and is accordingly regarded as the most acceptable form of fluid therapy in burn shock.[1] Although isotonic sodium chloride solutions have been used in burn shock with good results by many, including Davidson,[2, 3] it is felt that such a colloid-free solution is only temporarily effective in shock, presumably because the colloid osmotic pressure of the animal's serum proteins is diminished by the saline infusion, with subsequent leakage of the administered fluid from the blood stream. To remove this deficiency, various colloids have been dissolved in saline solution, among which may be mentioned gum acacia, gelatin, and, more recently, bovine and human serum albumin.

Recent work, however, suggests that the concept which emphasizes the colloidal osmotic pressure of serum proteins may be inadequate to explain the therapeutic activity of plasma or serum in certain types of shock. Thus, Mylon, Winternitz, and de Sütö Nagy[4] have presented evidence that there is a labile factor in plasma which, independent of colloid osmotic action, reduces mortality in tourniquet shock in dogs. We have found in animals,[5] as was independently observed by Rosenthal,[6] that sodium chloride has antiburn shock activity, thus confirming

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Aided by grants from the Blanche May Selden Fund, the Martha Kirschner Haft Memorial Fund, F. Brice, Morton May, Walter Kirschner, and Mr. and Mrs. S. Marx.
Received for publication July 3, 1944.

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150 to 200 grams, were scalded at 70° C. for ten seconds. The agents under investigation were administered approximately one hour after scalding (unless otherwise stated) to animals which were not at that time moribund, and a similar group, which received control solutions or no treatment, served as a control.

A. Influence of Route of Administration on Activity of Sodium Chloride.—In evaluating the influence of the route of administration on the therapeutic activity of sodium chloride, Rosenthal[7] concluded that intravenous administration was less effective than oral or intraperitoneal administration. In view of the importance of ascertaining whether the intravenous route is, in reality, less effective than the oral or intraperitoneal, the effectiveness of administering sodium chloride by these various routes has been evaluated by repeated testing.

In these experiments, mice were divided into five groups one hour after scalding; one group served as a control, and the other groups received 1 c.c. of 0.9 per cent sodium chloride solution either intravenously, intramuscularly, intraperitoneally, or orally. Table I gives the results obtained in four trials on 481 mice and in one experiment with forty-four rats. It will be seen that saline, independent of the route of administration, increased the average survival time and decreased the mortality. The average survival time was increased 84, 95, 100, and 69 per cent by giving isotonic salt solution by the intravenous, intraperitoneal, oral, and intramuscular routes, respectively, in the four experiments in which mice were employed. Although it might appear that the results with the intravenous and intramuscular routes were somewhat less satisfactory than with oral or intraperitoneal administration, these differences are not significant in view of the wide variation in the method. In individual trials, it will be seen that saline intravenously may be better, the same as, or worse than saline administered by mouth or intraperitoneally. The survival time was increased over the untreated controls by 28, 26, 31, and 17 per cent by administering saline by the intravenous, intraperitoneal, oral, and intramuscular routes, respectively. Again, these values are not significantly different. It is apparent that had only one experiment been performed, erroneous conclusions may have been derived, although it is possible by chance that correct evaluation may have been obtained. It would therefore seem that the route of administration has little effect upon the antiburn shock activity of sodium chloride.

B. Comparison of the Therapeutic Activity of Sodium Succinate and Sodium Chloride.—The fact that sodium chloride has therapeutic activity in this type of burn shock raises the question as to which ion is the important agent. In testing this point, an isotonic solution of sodium succinate was compared to isotonic sodium chloride; both solutions were given by mouth, one hour after scalding. Attention was given the possibility that the succinate possessed specific therapeutic activity in shock,

earlier clinical observations. In further studies, Rosenthal showed that, in mice, the therapeutic activity of sodium chloride in burn shock is dependent upon the sodium ion,[7] and that the therapeutic action of serum in tourniquet,[8] as well as burn, shock[7] can be explained in terms of the sodium content of the serum.

Therefore, it would appear that serum and plasma may be therapeutically active in shock because the administered fluid contains: (a) sodium, (b) proteins which possess colloid osmotic activity, or (c) the labile factor of Mylon and his co-workers. Having developed a standardized method for evaluating therapeutic agents in burn shock, we have studied the relative importance of the above factors with respect to the therapeutic activity of serum in shock.

In addition, evidence has been obtained on the following questions of practical importance. (a) Is water by mouth harmful, as claimed by some?[7] (b) Is sodium chloride more effective in burn shock when administered orally or intraperitoneally than by the intravenous route?[7]

METHOD

The details of the method used in these studies have been described in a previous report,[9] and may be summarized as follows. The time-mortality curves of groups of rats or mice treated with the agents under investigation are compared with those of suitable control groups after both groups have been subjected to thermal injury under identical conditions. Standardized thermal injury is administered by immersing the entire body, except the head and neck, of etherized animals into scalding water for definite periods of time. Anesthesia was complete, and the animals had no pain. The experiments are terminated forty-eight hours after the infliction of thermal injury, and the average survival time and the percentage of survivors are ascertained. It has been found, using groups containing as many as twenty to thirty animals, wherein variable factors, such as the degree of thermal injury, body weight, sex, strain, pre-experimental nutritional regime, and hydration, are adequately controlled, that variations in either the average survival time or in percentage mortality occur between untreated groups which are statistically significant. This means that a variable is operative in the method which may give rise to erroneous evaluation of antiburn shock activity. It is, therefore, apparent that an inactive substance, in a single test, using as many as thirty animals to a group, may appear to have therapeutic activity. Contrariwise, it is possible to obtain apparently negative results with a therapeutically active agent. However, it has been shown that, by doing a large number of experiments, this difficulty is overcome if therapeutic activity be evaluated by the consistency with which responses are obtained. Thus, an active therapeutic agent, on repeated testing, using groups of twenty to thirty animals, although it shows an occasional negative result, will, in the majority of tests, elicit positive responses; and conversely, inactive substances will show negative results in most tests, although occasional positive responses may be obtained.

In these experiments, the usual method of producing burn shock was to immerse anesthetized mice, weighing approximately 20 grams, for ten seconds in water at 65° C., whereas etherized rats, weighing from

in view of the report by Mylon, et al.,[4] that succinate treatment increased the survival time of dogs subjected to tourniquet shock.

Table II, *A* shows the results obtained on 331 mice in five trials. It will be seen that, on the average, sodium chloride increased the survival time 144 per cent, whereas sodium succinate increased it 146 per cent. The survival was increased 28 and 27 per cent by sodium chloride and sodium succinate, respectively. These data demonstrate that sodium succinate is as effective as, but is not superior to, sodium chloride. This confirms Rosenthal's contention concerning the importance of the sodium ion. Further, these data show that the succinate ion, in the dosages employed, is without benefit in scald shock.

C. Comparison of Isotonic Glucose With Sodium Chloride.—The question arises whether isotonic salt solution is useful in this type of shock by virtue of its sodium content, or because it is isotonic. To answer this question, the effectiveness of isotonic sodium chloride was compared to that of isotonic glucose, given intravenously.

Table II, *B* illustrates the results obtained on 478 animals in seven trials. It will be seen that glucose, on the average, increased the survival time 82 per cent, and the percentage of survivors, 8 per cent. Saline is more effective than glucose because the survival time was increased 124 per cent, and the percentage of survivors was increased 24 per cent. Saline was definitely active in five of the seven trials, whereas glucose was superior to the control in only three of seven instances. In comparing glucose and saline, it was observed that glucose was definitely inferior in five of the seven trials. These data, therefore, demonstrate that, although glucose is somewhat effective, an equivalent volume of

TABLE II

INFLUENCE OF VARIOUS SOLUTIONS ON SCALD SHOCK

PROCEDURE	NUMBER OF TRIALS	TOTAL NUMBER OF MICE	MEAN OF AVERAGE SURVIVAL TIME (HR.)	MEAN OF PERCENTAGE OF SURVIVORS	MEAN OF PERCENTAGE INCREASE IN AVERAGE SURVIVAL TIME OVER CONTROLS	MEAN OF INCREASE IN PERCENTAGE OF SURVIVORS OVER CONTROLS
A						
No treatment		113	14.7	13		
Saline	5	109	35.9	41	144	28
Sodium succinate		109	36.1	40	146	27
B						
No treatment		164	15.2	15		
Saline	7	151	34.0	41	124	26
Glucose		160	27.5	23	81	8
C						
No treatment		174	15.9	18		
Saline	7	158	27.8	41	75	23
Water		163	21.8	32	37	14
D						
No treatment		113	14.7	13		
Glucose	5	99	31.6	26	115	13
Glucose-gelatin		95	20.9	13	42	0

TABLE I

ADMINISTRATION OF ISOTONIC SALINE BY DIFFERENT ROUTES

ANIMAL	NO TREATMENT			INTRAVENOUS			INTRAPERITONEAL			ORAL			INTRAMUSCULAR		
	NUMBER OF ANIMALS	AVERAGE SURVIVAL TIME (HR.)	SURVIVORS (%)	NUMBER OF ANIMALS	INCREASE IN SURVIVAL TIME (%)	INCREASE IN SURVIVORS (%)	NUMBER OF ANIMALS	INCREASE IN SURVIVAL TIME (%)	INCREASE IN SURVIVORS (%)	NUMBER OF ANIMALS	INCREASE IN SURVIVAL TIME (%)	INCREASE IN SURVIVORS (%)	NUMBER OF ANIMALS	INCREASE IN SURVIVAL TIME (%)	INCREASE IN SURVIVORS (%)
Mice	25	19.9	32	24	97	43	25	81	28	25	83	32	25	39	4
	23	20.4	30	23	43	18	23	62	22	23	86	35	23	56	14
	22	7.7	0	22	136	9	22	173	14	21	168	19	21	130	14
	28	26.0	36	27	61	42	27	63	38	27	61	38	28	53	36
Rats	11	6.9	0	11	195	36	11	485	82	11	224	27			

strongly suggests that the colloid osmotic activity of protein in this form of burn shock has little influence on survival. To check this conclusion, the effect of gelatin was ascertained, for gelatin possesses colloid osmotic activity and is useful as a plasma substitute.[10, 11]

The gelatin solution used in these experiments was prepared by autoclaving a 5 per cent solution of gelatin (Wilson), dissolved in isotonic glucose solution (5.5 per cent) for fifteen minutes at 25 pounds' pressure. The effectiveness of this gelatin-glucose solution in decreasing mortality was compared to that of a solution of glucose, employing mice as the test animals. The solutions were injected intravenously, approximately one hour after thermal injury.

The results obtained on 307 mice are shown in Table II, *D*; they demonstrate that the addition of gelatin to isotonic glucose solution does not increase the therapeutic activity, as should be the case if the colloid osmotic activity of protein were important in this type of burn.

DISCUSSION

Using the scalding method for the production of burn shock, it has been found on repeated testing that isotonic sodium chloride solution is equally effective when administered intravenously, intraperitoneally, intramuscularly, or orally. This contradicts the contention that saline intravenously is less effective than equivalent volumes administered by the oral or intraperitoneal route.[7]

In comparing the therapeutic activity of sodium chloride with sodium succinate, equivalent results were obtained, as has been previously reported by Rosenthal, thus confirming the view that the sodium, and not the chloride, ion is responsible for the therapeutic response obtained with saline.[7] In view of the report that succinate is therapeutically useful in tourniquet shock,[4] the demonstration that sodium succinate was not superior to sodium chloride serves to indicate that succinate, in the doses employed, was without specific therapeutic value in this type of shock.

The fact that isotonic glucose solution, although it is effective in decreasing mortality, is less active than an equivalent volume of sodium chloride demonstrates that the activity of the sodium is not merely one of simple replacement of isotonic fluid, and suggests that the sodium has a specific action in combating this type of burn shock. The fact that glucose is helpful may be due in part to simple fluid replacement or to a possible specific effect of glucose.

It has been found that the oral administration of water is not toxic, as some believe,[7] but may possibly be of some benefit.

Finally, it has been shown in this type of burn shock that the intravenous administration of protein, which has colloid osmotic activity, does not influence survival after thermal injury, for it has been shown

sodium chloride has a therapeutic action over and above that of fluid replacement, as represented by glucose administration. The results with glucose do not permit conclusions to be drawn as to whether the glucose or the fluid is responsible for the decreased mortality observed.

D. Effect of Water by Mouth.—In view of the fact that many patients in shock are thirsty, it is important to know the effect of the oral administration of water. Does water help in shock, or is it actually deleterious, as has been reported?[7] To obtain information on this point, the effect of giving water by mouth was compared with that of orally administered isotonic salt solution.

Table II, *C* shows the results obtained on 495 animals in seven trials. It is evident from repeated testing that, although water is less effective than saline, it is, nevertheless, not toxic. On the contrary, water may slightly decrease mortality, although the data are not sufficient to draw a final conclusion regarding this point.

E. Comparison of Homologous Serum With Sodium Chloride.—It has generally been held that serum or plasma is therapeutically superior to saline intravenously in burn shock. This view, however, is not supported by Rosenthal,[7] who, in a single trial, showed that saline was as effective as homologous serum in decreasing mortality among mice after scalding. It was important to ascertain whether or not saline is actually as effective as serum in this type of burn shock.

In these experiments, rats were the test animals. Rat serum was compared to an equivalent volume of saline, and both solutions were given via the tail vein after scalding. Table III shows the results obtained on 216 animals. It will be seen that, under the conditions of these experiments, saline was as effective as serum, and it thus appears that the therapeutic activity of serum can be ascribed to its sodium content.

F. Comparison of Gelatin-Glucose With Isotonic Glucose Solution.—The fact that saline was as effective as serum in reducing mortality

TABLE III

RELATION OF INTRAVENOUS ADMINISTRATION OF SALINE AND SERUM TO SCALD SHOCK

PROCEDURE	FLUID INJECTED AS PERCENTAGE OF BODY WEIGHT	TIME OF INJECTION AFTER SCALDING (HR.)	NUMBER OF RATS	AVERAGE SURVIVAL TIME (HR.)	SURVIVORS (%)	INCREASE IN AVERAGE SURVIVAL TIME OVER CONTROLS (%)	INCREASE IN PERCENTAGE OF SURVIVORS OVER CONTROLS
No treatment			21	10.6	5		
Saline	4%	1.0	29	24.8	28	134	23
Serum			28	22.8	21	115	16
No treatment	2%	1.5	13	12.7	15		
Saline	(adminis-	and	46	27.4	39	116	24
Serum	tered twice)	4.5	41	31.2	34	146	19
Saline			19	27.2	32		
Serum	2%	1.5	19	25.3	16		

CONCLUSIONS

1. Sodium chloride has therapeutic activity in burn shock, and the therapeutic agent appears to be the sodium ion.

2. Sodium chloride appears to be equally effective when administered by the intravenous, oral, intraperitoneal, or intramuscular routes.

3. The therapeutic activity of sodium chloride cannot be explained as due to simple fluid replacement, for equivalent volumes of isotonic glucose are less effective.

4. The oral administration of water is not deleterious, and may actually be of slight benefit.

5. The therapeutic activity of serum appears to be due to its content of sodium, for it has been shown that (a) serum is no more effective than equivalent volumes of saline, and (b) the colloid osmotic activity of gelatin solutions has no influence on mortality.

6. There does not seem to be a specific antishock factor in serum.

7. These conclusions hold for the specific type of shock in rats and mice which follows scalding, and cannot as yet be applied to other forms of shock.

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that saline is as effective as serum and that the addition of 5 per cent gelatin to isotonic glucose solution does not enhance the therapeutic effect. It may be pointed out that if there is a labile factor in plasma which exerts some specific therapeutic action in shock, as Mylon, Winternitz, and de Süto Nagy[4] have suggested, these experiments demonstrate no such activity in serum in scald shock.

In considering the significance of these results for clinical burn shock, it should be emphasized that the method employed in these studies subjects a relatively large surface of the body to relatively low temperatures, varying from 65° to 75° C. On the other hand, burns by very high temperatures, involving a relatively small surface of the body, also produce shock. In the latter instance, injury to tissues beneath the skin occurs, whereas, with low temperature burns, the damage produced in our experiments was restricted to superficial tissues. It does not necessarily follow that, because shock develops in both instances after thermal injury, the mechanism of shock production is similar. Elman[12] has also suggested this difference.

With this point of view, the results of this study may prove to be applicable to the clinical shock which follows superficial burns involving large areas of the body. In this type of burn, it would appear that saline treatment should be effective by all routes of administration. There would appear to be no necessity to administer isotonic sodium salt solution in clinical burn shock by the oral route exclusively, as has been so successfully done by Fox,[13] for the view that intravenous treatment is ineffective has been shown in this study not to be tenable. Although the oral route admittedly has marked advantages over other routes of administration in those instances in which, for one reason or another, salt solution cannot be given by mouth (i.e., patients with burns involving the mouth, throat, etc., or patients with persistent vomiting), the intravenous route, combined with hypodermoclysis, may possibly be used advantageously. In most instances, however, the treatment advocated by Fox would appear to be most efficacious for practical purposes.

There would appear to be no contraindication to the administration of water because of a postulated toxic action, for it has been shown that water is without toxic effect, and may, in fact, be of slight value. Water, however, is much inferior to the oral administration of isotonic salt solution.

It must be emphasized that the above conclusions are applicable to the shock resulting from this type of experimental thermal injury. Although Rosenthal[8] has shown that a similar situation may exist in tourniquet shock, it would appear premature to apply these suggestions to all types of shock. It is possible that shock due to burns may be of several types, and each type may require a different kind of therapy. At the present time, we are investigating this point.

TABLE I

EFFECT OF NEPHRECTOMY ON RESISTANCE TO BURN SHOCK

PROCEDURE	NUMBER OF RATS	AVERAGE SURVIVAL TIME (HR.)	SURVIVORS (%)	TIME OF 50% MORTALITY (HR.)	INCREASE IN AVERAGE SURVIVAL TIME OVER CONTROLS (%)	INCREASE IN SURVIVORS OVER CONTROLS (%)
Nephrectomy	15	29.7	0	21		
Sham	15	40.3	87	(48 – 13%)	-26	-87
Nephrectomy	11	23.4	0	16		
Sham	10	40.0	60	(48 – 40%)	-42	-60
Nephrectomy	15	21.0	0	16		
Sham	15	36.5	53	(48 – 47%)	-42	-53
Nephrectomy	10	19.2	0	16		
Sham	10	45.6	70	(48 – 30%)	-58	-70
Nephrectomy	10	16.5	0	16		
Sham	10	33.0	30	40	-50	-30
Nephrectomy	10	27.6	0	23		
Sham	10	43.2	70	(48 – 30%)	-36	-70
Nephrectomy	10	23.9	0	16		
Sham	10	44.8	90	(48 – 10%)	-47	-90
Nephrectomy	10	24.5	0	16		
Sham	10	34.4	50	40	-29	-50

Table I show that nephrectomized animals uniformly had a significant decrease in percentage of survival rate and a decrease in the average survival time.

The above experiments demonstrate that nephrectomized animals have decreased resistance to thermal injury. However, it would be erroneous to conclude from these data that this lowered resistance is due to the absence of the renal pressor system. It is evident that removal of the kidneys also removes their excretory function, and it is therefore possible that the differences observed could be due to the effect of renal excretory insufficiency.

Experiment 2. Comparison of Nephrectomized and Ureter-Ligated Rats.—To ascertain whether the decreased resistance of nephrectomized rats to scalding is due to removal of the renal pressor system or to excretory insufficiency, ureter-ligated rats were compared to nephrectomized animals. The experiment was designed to produce an approximately equal degree of excretory insufficiency, but the ureter-ligated animals possessed an intact, but perhaps not completely functioning, renal pressor system. Therefore, if the renal pressor system has antiburn shock activity, the ureter-ligated animals should be able to withstand shock due to burns better than the nephrectomized animals.

To test this point, four experiments, using a total of one hundred seventeen rats, were performed. The ureter ligations were performed through bilateral lumbar incisions; the ureters were ligated near the renal pelvis. Since ureter ligation does not produce immediate excretory insufficiency, because for a short while urine is excreted into the renal pelvis, the ureter ligations were performed five to six hours prior to scalding, whereas the nephrectomized rats were burned three to four hours after the operation.

THE ROLE OF THE RENAL PRESSOR SYSTEM IN BURN SHOCK

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IT HAS been recently shown that, in certain hypotensive states, renin is released from the kidneys.[1-3] This may represent a homeostatic mechanism for maintaining arterial pressure, and would appear to be important in the hypotension which often accompanies shock. In fact, Bahnson[4] found that nephrectomized rats had a greater fall in arterial pressure and died after the removal of smaller amounts of blood than did sham-nephrectomized controls. A priori, one might not expect that the renal pressor system would be of great importance because of tachyphylaxis due to the rapid exhaustion of hypertensinogen. Having developed a method for producing standardized shock,[5] we undertook experiments to ascertain whether or not the renal pressor system has any effect on survival time and mortality of rats subjected to a scalding burn.

Experiment 1. Effect of Nephrectomy on Resistance to Burn Shock.—If the renal pressor system is important in combating shock due to thermal injury, nephrectomized animals which are unable to secrete renin should be less resistant than animals with intact kidneys. This lowered resistance should be evidenced by an increased mortality and a decreased survival time after thermal injury.

Long-Evans rats, weighing 150 to 265 grams, were used in these and subsequent experiments. The animals were etherized, and the kidneys were removed through lumbar incisions. The control animals for this experiment were sham nephrectomized in a manner designed to reproduce the trauma and manipulation involved in the nephrectomy operation.

Three to four hours after the operation, the resistance of nephrectomized and sham-nephrectomized animals to burn shock was evaluated by the following procedure. The entire body, except the head and neck, of etherized animals was immersed in water at 70° C. for ten seconds. After the scalding, the two groups were separated, placed in cages, and observations on survival were made during the next forty-eight hours. The time mortality curves for both nephrectomized and sham-nephrectomized animals were compared in eight experiments, using a total of ninety-one nephrectomized rats and ninety control rats. The data in

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Aided by grants from the Blanche May Selden Fund, the Martha Kirschner Haft Memorial Fund, F. Brice, Morton May, Walter Kirschner, and Mr. and Mrs. S. Marx.
Received for publication July 3, 1944.

TABLE IV

EFFECT OF NEPHRECTOMY IN SEVERE SHOCK

PROCEDURE	SCALDING TEMPERATURE (° C.)	CONDITIONS TIME (SEC.)	NUMBER OF RATS	AVERAGE SURVIVAL TIME (HR.)	SURVIVORS (%)	TIME OF 50% MORTALITY (HR.)	INCREASE IN AVERAGE SURVIVAL TIME OVER CONTROLS (%)	INCREASE IN SURVIVORS OVER CONTROLS (%)
Nephrectomy	90	20	21	3.3	0	3.0	0	0
Sham			21	3.3	0	3.0		
Nephrectomy	85	20	10	4.1	0	3.5	–24	0
Sham			10	5.4	0	4.0		
Nephrectomy	80	15	9	10.0	0	4.5	– 1	0
Sham			7	10.1	0	4.0		
Nephrectomy	75	15	13	12.4	0	8.0	– 7	0
Sham			11	13.3	0	8.0		
Nephrectomy	75	10	10	20.2	0	16.0	–10	–20
Sham			10	22.4	20	16.0		

TABLE II

COMPARISON OF NEPHRECTOMIZED AND URETER-LIGATED RATS

PROCEDURE	NUMBER OF RATS	AVERAGE SURVIVAL TIME (HR.)	SURVIVORS (%)	TIME OF 50% MORTALITY (HR.)
Nephrectomy	20	37.9	45	40
Ureter-Ligated	20	32.7	0	40
Nephrectomy	15	23.0	0	22
Ureter-Ligated	15	26.0	0	14
Nephrectomy	15	17.0	0	14
Ureter-Ligated	15	16.0	0	14
Nephrectomy	12	27.1	0	19
Ureter-Ligated	5	15.0	0	16

The results obtained in this experiment are shown in Table II. It will be seen that the ureter-ligated animals did not exhibit superior resistance to scald shock, as compared with nephrectomized rats. Nonprotein nitrogen estimations performed on preagonal animals revealed equally marked elevations in both groups.

These results demonstrate that the renal pressor system, which is present in ureter-ligated animals, had no effect on resistance to burn shock. Although ureter ligation is said to stimulate the renal pressor system, temporarily at least, with resultant hypertension,[6] evidence has also been presented that, in more prolonged experiments, ureter ligation may inhibit the renal pressor system.[7] This experiment would seem to demonstrate that the renal pressor system is unimportant, for animals with an intact renal pressor system and renal excretory insufficiency were not more resistant than animals with an equal degree of excretory insufficiency.

Experiment 3. The Effect of Renal Excretory Insufficiency.—In the first experiment, it was shown that nephrectomized rats are less able to withstand thermal trauma than are sham-nephrectomized rats. It was suggested that this could have been due to renal excretory insufficiency. Examination of the data revealed that the nephrectomized animals died, in the majority of instances, between sixteen and forty hours after trauma; the average was twenty-four hours. In order to ascertain whether the lowered resistance to trauma was due to renal insufficiency, the effect of this factor was studied in the following manner. It was felt that if impairment of the renal excretory function was important, animals nephrectomized twenty-four hours previously should be more

TABLE III

EFFECT OF RENAL EXCRETORY INSUFFICIENCY

SCALDING TIME AFTER NEPHRECTOMY (HR.)	NUMBER OF RATS	AVERAGE SURVIVAL TIME (HR.)	SURVIVORS (%)	TIME OF 50% MORTALITY (HR.)
4	12	40.6	33	40
24	11	19.6	0	16
4	12	27.1	0	19
24	12	13.6	0	16

or to the operation of the renal pressor system. It was next shown that, if the factor of renal insufficiency was controlled by comparing ureter-ligated animals with nephrectomized animals, the presence of the renal pressor system was ineffective, for no difference was observed. Next, it was demonstrated that a twenty-four-hour period of renal insufficiency markedly decreased resistance to burn shock, thus explaining the decreased resistance of the nephrectomized animals in the experiments of longer duration. Finally, it was shown that there is no difference between nephrectomized and sham-nephrectomized animals if they are traumatized sufficiently to kill the animal before renal insufficiency becomes marked.

These results, demonstrating the ineffectiveness of the renal pressor system in burn shock, do not disprove the existence of the renal pressor system. However, it is clear that, in the type of trauma employed in these experiments, this system had no influence on survival. Whether or not the renal pressor system may have raised the blood pressure of our animals was not ascertained.

Renal excretory insufficiency has been found to occur quite frequently in shock, and, because of its deleterious effect, attempts should be made to control this factor in the treatment of patients in shock.

CONCLUSIONS

1. It was found that the renal pressor system has no influence on either mortality or survival time in burn shock.

2. Renal excretory insufficiency decreases the resistance of animals to burn shock. This factor should be considered in the treatment of patients in shock.

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sensitive to thermal trauma than animals nephrectomized only a short while prior to trauma.

The results of two experiments, using a total of forty-seven animals, are shown in Table III. It will be seen that rats which were nephrectomized twenty-four hours previously were markedly less resistant than recently nephrectomized rats. This, then, demonstrates that a period of twenty-four hours of anuria significantly decreases the ability to withstand burn shock, and explains the decreased resistance of nephrectomized animals observed in Experiment 1. In passing, it may be of interest to point out that this observation may be of clinical significance, for it might explain the low resistance of patients with severe renal insufficiency to operative procedures.

Experiment 4. Effect of Nephrectomy in Severe Shock.—To provide further evidence for the view that the decreased resistance of the nephrectomized animals in Experiment 1 was due to renal insufficiency, and not to the absence of the renal pressor system, the following experiment was performed. By increasing the degree of thermal injury, animals are made to develop shock and die rapidly. If, under these conditions, nephrectomized rats be compared with sham-nephrectomized controls, the factor of renal insufficiency becomes less important because the animals die before the renal insufficiency becomes marked. If the renal pressor mechanism is effective, sham-nephrectomized rats should be more resistant than nephrectomized rats under these circumstances.

Five experiments were performed in which nephrectomized and sham-nephrectomized animals were anesthetized and then scalded at temperatures varying from 75° C. to 90° C. from ten to twenty seconds. These conditions produce a greater degree of thermal injury than that obtained in all of the previous experiments. This is evident from the fact that the control animals died rapidly, with an average survival period varying from three to twenty-three hours, in contrast to Experiment 1, in which the average survival time varied from thirty-three to forty-five hours.

The results (Table IV) show that, under these conditions of rapid mortality, there is no significant difference between nephrectomized and sham-nephrectomized rats. Thus it is clear that, when the factor of renal insufficiency is largely eliminated, the renal pressor system of the sham-nephrectomized rats had no significant effect upon mortality and survival time.

DISCUSSION

Experiments were designed to ascertain the role of the renal pressor system in scald shock. It was first found that nephrectomized animals appeared to be less resistant to shock than control animals when the degree of thermal injury was such that the control animals died with average survival periods of thirty-three to forty-five hours. It was thought that this might be due to either the effect of renal insufficiency

the rats become exceedingly irritable. When such a rat is placed in a separate cage, it will bite its cyanotic limbs; or, if several rats are placed in the same cage, the animals will bite one another. The amount of blood loss suffered is nil when the circulation is occluded, but, upon release of the tourniquet and subsequent reactive hyperemia, the amount of hemorrhage through these bites may be considerable. When no precautions were taken to prevent this hemorrhage, it was observed in thirty cases that rats subjected to five-hour hind-leg ischemia regularly died after release of the tourniquets. When, however, biting, and, therefore hemorrhage, was prevented by sewing the rats' lips together, thirty animals whose hind-leg blood flow was obstructed for five hours showed only an 80 per cent mortality after release of the tourniquets. This indicates that removal of the extraneous hemorrhage factor permits survival that otherwise does not occur.

B. Effect of food and water: Since Hechter, Krohn, and Harris[1] previously reported zero mortality in ten rats subjected to five-hour tourniquet obstruction of both hind legs when the animals were allowed access to food and water, the effect of permitting animals to eat and drink after tourniquet removal was ascertained. In a series of sixty-four rats the mouth sutures were opened after tourniquet removal and the animals were allowed access to food and water, and it was found that the mortality was only 20 per cent. Remembering that the mortality was 80 per cent when the rats were not allowed access to food and water, this serves to indicate that markedly different results are obtainable, depending upon whether or not the animals are permitted to eat and drink.

C. Shocklike death without removal of the tourniquets: It was observed in six instances that the animals died in a shocklike state *before the tourniquets on the hind legs were removed.* In all of these cases, the hind legs were markedly cyanotic and were not edematous. Intra-aortic injection of concentrated trypan blue solution, shortly after the animals expired, produced staining of the tissues above, but not below, the tourniquet, demonstrating that the blood flow to these limbs was effectively occluded. The fact that death occurs in animals before the tourniquet is removed is not explicable in terms of local fluid loss, nor is it likely that death was due to toxic substances formed in the ischemic areas distal to the tourniquet. The possibility that the shock state developed as a result of muscle crushing above or beneath the tourniquet seems unlikely, for the area damaged in this fashion by a rubber band is relatively small, and previous work[5] has shown that large areas of muscle in rats may be traumatized without the development of shock.

D. Edema in occluded limbs before removal of obstruction: Although the rubber bands were tied tightly in all instances, it was observed that some animals developed significant edema in one or both of the obstructed limbs before the tourniquets were removed. This

FURTHER STUDIES ON THE LIVER PRINCIPLE WHICH IS EFFECTIVE AGAINST BURN SHOCK

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In previous work from this laboratory, it has been shown that there is a principle in liver extract which, when administered intraperitoneally or subcutaneously prior to thermal injury, significantly decreases the acute mortality and prolongs the survival time of rats and mice subjected to a standardized scalding procedure.[1] The present work was undertaken to ascertain whether liver exerts activity in types of shock other than that produced by scalding. We have, therefore, attempted to evaluate the action of liver extract in the shock produced by subjecting rats to temporary hind-leg ischemia; to an exudative inflammatory reaction, "medical shock"; and to hemorrhage. In addition, data are presented which demonstrate that liver extract is active in burn shock when administered by mouth prior to thermal injury.

EFFECT OF LIVER EXTRACT IN TOURNIQUET SHOCK

It has been regularly observed in tourniquet shock experiments that shock does not develop while the tourniquet is in place but occurs only after removal of the obstruction to blood flow.[2-4] The shock which develops after release of the tourniquets has been ascribed (a) to local fluid loss into the damaged limbs, for the application of casts to the ischemic limbs prevents shock;[3] and (b) to the release of toxic shock-producing factors formed in the ischemic areas into the general circulation.[2, 4] Since ischemic limbs of dogs may become infected, and air may accumulate under the skin,[3] the question whether the hypothetical toxic factor is primarily the result of the abnormal metabolism of ischemic tissues or is due to bacterial infection becomes important and has yet to be clearly answered.

After subjecting several hundred rats to tourniquet shock, it was observed that there are several complicating features, not mentioned in the literature, which are associated with this shock-producing procedure. These will be discussed separately.

Complicating Features.—

A. Hemorrhage from bites after removal of tourniquets: When rubber-band tourniquets are placed around the thighs of both hind legs,

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Aided by grants from the Blanche May Selden Fund, the Martha Kirschner Haft Memorial Fund, F. Brice, Morton May, Walter Kirschner, and Mr. and Mrs. S. Marx.

Received for publication July 3, 1944.

TABLE II

EFFECT OF LIVER EXTRACT UPON BACTERIAL SEPTICEMIA

ORGANISM	TREATMENT	NUMBER OF MICE	MEAN SURVIVAL TIME (HR.)	STANDARD ERROR
Staph. aureaus	Control	20	10.1	±2.3
	Liver	20	13.3	±2.7
Pneumococcus Type III	Control	57	25.3	±0.6
	Liver	57	22.3	±0.6
Suspension of feces	Control	80	19.8	±1.1
	Liver	80	19.9	±1.2

mice died after the injection of bacterial agents, contrary to our expectations, peritoneal exudates were not observed. The deaths were due to bacteremia; positive cultures were regularly obtained from the blood of the infected animals. The effect of liver extract treatment in this type of condition is shown in Table II; it will be seen that liver had no effect. Since little or no exudation was produced by these agents, no conclusions may be drawn regarding the action of liver extract in the shock which is associated with exudative inflammatory states. These data do indicate, however, that the shock associated with bacteremia induced by these organisms is not modified by liver treatment. It is of interest that it has recently been demonstrated that certain types of shock after muscle crushing experiments on dogs are of bacterial origin.[6] It would seem unlikely that liver extract, since it has no antibacterial action, would be effective in those types of shock in which bacteria are of primary importance.

Effect of Liver Extract After Hemorrhage.—It was observed that anesthetized rats could be bled more conveniently by severing the femoral artery with a sharp blade than by bleeding from the tail, by heart puncture, or by withdrawing blood from the femoral artery with a syringe. Using this technique, the degree of hemorrhage was ascertained by absorbing the blood on weighed cotton swabs.

The response of anesthetized rats to a single hemorrhage was found to depend not only upon the degree of exsanguination, but also upon the anesthetic employed. Thus, when ether was used, the degree of hemorrhage necessary to produce 50 per cent mortality varied from 2.7 to 3.2 per cent of the body weight. In nembutalized rats, however, hemorrhages ranging from as little as 2.3 to 2.5 per cent of the body weight proved to be uniformly fatal. Ogden has made similar observations.[7]

After bleeding etherized rats, the animals either (a) recovered immediately and survived indefinitely; (b) died within thirty minutes and showed, during this interval, symptoms of cardiovascular and respiratory distress (this is death due to acute exsanguination, and is not hemorrhagic shock); or (c) apparently recovered but then gradually declined and eventually died in a shocklike state. The effect of hemorrhage on nembutalized rats differed markedly from the results ob-

suggests that occlusion of the arterial circulation by the tourniquet was not complete in these animals.

Effect of Liver Extract.—Taking the above factors into account, the effect of liver extract upon tourniquet shock was studied in the following manner: Etherized animals' lips were sewed together, and rubber-band tourniquets were tied tightly around both hind legs. Four and one-half hours later, the animals were divided into two groups. One group received 1 c.c. of 15-unit liver extract intraperitoneally per 100 grams of body weight; the other group received an equal volume of 0.5 per cent phenol solution by the same route. The animals were not allowed food or water. One-half hour after the injection, the ties were removed and survival observations were made. Four experiments, comprising the results on 155 rats, are shown in Table I; it is evident that liver extract treatment did not significantly alter the mortality of tourniquet shock in rats.

TABLE I

EFFECT OF LIVER EXTRACT ON THE MORTALITY PRODUCED BY TOURNIQUET SHOCK

EXPERIMENT	TREATMENT	NUMBER OF RATS	NUMBER LIVED	NUMBER DIED	MORTALITY (%)
1	Liver	12	6	6	50
	Control	11	6	5	45
2	Liver	19	4	15	79
	Control	19	4	15	79
3	Liver	19	15	4	21
	Control	19	12	7	37
4	Liver	28	8	20	72
	Control	30	11	19	63
Totals	Liver	78	33	45	58
	Control	77	33	46	60

The shock which follows tourniquet removal is apparently due to a complicated series of reactions which may be modified by many variables. In these experiments, factors such as hemorrhage from bites, nutrition and hydration, and environmental conditions were controlled; however, uncontrollable variables, such as edema, the unknown factor which occasionally led to death before tourniquet removal, and possible variable degrees of infection were still operative. The fact that liver extract was not effective in this form of shock demonstrates that shock-producing mechanisms which are not modified by liver extract treatment are responsible for death. However, the complexity of the tourniquet-shock syndrome permits no conclusions on this point, and it would be desirable to retest liver extract on tourniquet shock with all variables adequately controlled.

Attempts to Produce Shock by Exudative, Bacterial Inflammation.—In an attempt to simulate the shock which follows infectious states associated with a large amount of exudation, such as occurs in peritonitis, mice were injected intraperitoneally with pure cultures of either *Staphylococcus aureus*, pneumococci, or a suspension of feces. Although the

tained on etherized rats in that death occurred after a prolonged period of decline which was similar to shock. It seemed clear, therefore, that the shocklike state observed in nembutalized rats was due in part to the nembutal. Since it seemed possible to attribute death under these conditions to an impairment by hemorrhage of the mechanisms involved in the removal or destruction of nembutal, as well as to hemorrhagic shock, we preferred not to use this method, although Engel, Winton, and Long[8] have made excellent observations regarding biochemical changes which occur in the shocklike state which occurs when nembutalized rats are subjected to hemorrhage.

In testing 15-unit liver extract on etherized rats it was observed that liver extract treatment did not alter the percentage mortality or the average survival time of the animals subjected to a single large hemorrhage. However, since the deaths which occurred were due to acute exsanguination, these data have little significance as regards the effect of liver in hemorrhagic shock.

It may be of interest that there was no effect of liver extract treatment upon the bleeding volume, as measured in etherized rats, using the aforementioned technique.

Effect of Orally Administered Liver Extract on Burn Shock.—The effect of orally administered liver extract on burn shock was evaluated, using the scalding method described previously in full detail.[1] Mice weighing approximately 20 grams were divided into two groups of at least twenty animals per group, and received, by stomach tube, either 1 c.c. of Lederle's 15-unit liver extract (which had been extracted with ether to remove the phenol preservative), or 1 c.c. of water. One-half hour later, the groups of mice were anesthetized with ether and scalded under identical conditions; the average survival time and the percentage mortality were ascertained. Six experiments of this type were performed; the usual condition of the scalding was an immersion period of ten seconds at 65° C. Experiment 7 was performed with a 1 per cent sodium chloride solution, instead of water, as a control.

Table III shows the results obtained on 325 mice. Examination of the data reveals that liver extract treatment by mouth decreased the mortality 32 per cent, and increased the survival time 98 per cent.

SUMMARY

These experiments demonstrate that liver extract, which has significant antiburn shock activity, either when administered parenterally, as in previous work,[1] or orally, as in the present study, is without comparable activity in the shock states which follow hind-leg ischemia or bacterial infection. It has been demonstrated that the mechanism of tourniquet shock in rats is complicated by several factors which are difficult to control. Before a final conclusion regarding the ineffectiveness of liver extract in this type of shock could be drawn, it would appear necessary that complicating factors be controlled. The nega-

TABLE III

EFFECT OF ORALLY ADMINISTERED LIVER EXTRACT UPON SCALD SHOCK

	ORAL WATER CONTROL			ORAL LIVER TREATMENT				
EXPERIMENT	NUMBER OF MICE	AVERAGE SURVIVAL TIME (HR.)	SURVIVORS (%)	NUMBER OF MICE	AVERAGE SURVIVAL TIME (HR.)	SURVIVORS (%)	INCREASE IN AVERAGE SURVIVAL TIME (%)	INCREASE IN SURVIVORS (%)
1	23	28.0	35	24	45.0	75	+61	+40
2	23	31.6	43	24	35.1	46	+11	+3
3	25	17.3	24	22	41.5	73	+14	+49
4	24	16.8	13	23	32.3	33	+92	+20
5	24	16.0	21	24	44.3	67	+177	+46
6	24	21.8	21	24	39.5	58	+81	+37
7*	20	20.4	15	21	42.4	67	+108	+52

*Oral 1 per cent sodium chloride control instead of oral water control.

INEFFECTIVENESS OF ADRENOCORTICAL HORMONES, THIAMINE, ASCORBIC ACID, NUPERCAINE, AND POST-TRAUMATIC SERUM IN SHOCK DUE TO SCALDING BURNS

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WITHIN recent years, many substances have been reported to be therapeutically effective in certain types of experimental shock. Among these may be mentioned adrenocortical hormones, thiamine, ascorbic acid, nupercaine, and posttraumatic convalescent serum. Although some of these agents, on being tested in later work, have been found to be inactive by some workers, the effectiveness of other agents has been neither confirmed nor denied.

In previous work,[1] using the scalding method for evaluating therapeutic activity in burn shock, it was discovered that considerable group variation is encountered when apparently identical groups of untreated rats or mice were subjected to standardized thermal injury under identical conditions. These variations were observed in groups containing as many as twenty to thirty animals, and the differences between the untreated groups were statistically significant. It is apparent that, in any single experiment, the differences between a treated and a control group which appear to give rise to statistically significant results could be due to chance. In order to overcome this difficulty, the evaluation of therapeutic activity was made only after repeated testing.

Although it is not possible to state definitely that other methods which have been utilized to test antishock agents are subject to an equal degree of variability, the fact that the scalding method permits adequate control of variables such as the degree of thermal injury, body weight, strain, and environmental conditions both prior to and after thermal injury, which is not always obtainable with other methods, strongly suggests that they likewise may prove to possess significant variation equal to, if not greater than, that observed with the scalding method. Upon examining the literature, it would appear that insufficient attention has been given to the variations inherent in shock-producing procedures, and, in many instances, conclusions regarding therapeutic activity appear to have been derived from an insufficient number of tests. It is possible that some of the confusion and the controversial reports regarding therapeutic agents in shock may be explained in this way.

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Aided by grants from the Blanche May Selden Fund, the Martha Kirschner Hiff Memorial Fund, F. Brice, Morton May, Walter Kirschner, and Mr. and Mrs. S. Marx.
Received for publication July 3, 1944.

tive results obtained with liver extract after acute exsanguination permit no conclusions to be drawn regarding liver activity in hemorrhagic shock.

The fact that liver is effective in burn shock, but not in tourniquet or bacterial shock, is further evidence for the concept that there are different mechanisms responsible for various types of shock, although all may give rise to a similar terminal picture. It further indicates that therapeutic measures must be evaluated individually for each type of shock, and that results obtained with one type of shock cannot be justifiably transferred to other types of shock.

CONCLUSIONS

1. Liver extract has significant antiburn shock activity when administered orally.
2. Liver extract has no therapeutic effect in certain types of bacteremia in mice.
3. Tourniquet shock in rats is due to the operation of complex mechanisms which are difficult to control.
4. Liver extract was found to be ineffective in tourniquet shock, and had no therapeutic effect in acute exsanguination.

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indicates that cortical hormone therapy produces no significant effect.[20] In experimental burn shock in mice, Rosenthal[21] found that neither cortical extract nor desoxycorticosterone had significant antishock activity. Although much work has been done on the use of desoxycorticosterone and cortical hormones in the prevention and treatment of shock in man, the results are conflicting and difficult to evaluate because of the nature of this type of experimentation.

A. Effect of Desoxycorticosterone Acetate.—The effect of desoxycorticosterone acetate was tested in five trials on mice, using 158 mice, and in two trials on 87 rats. The dose of desoxycorticosterone was 5 and 2.5 mg. per 100 grams of body weight for rats and mice, respectively, and the drug was injected intraperitoneally one-half hour prior to thermal injury. The desoxycorticosterone used in these experiments was dissolved in sesame oil to make a solution containing 5 mg. per cubic centimeter. As a control for the desoxycorticosterone-treated animals, groups of rats and mice received an equivalent volume of sesame oil. The results are shown in Fig. 1, *A;* under the conditions of these experiments, desoxycorticosterone was without significant effect upon mortality in scald shock.

B. Effect of Adrenal Cortex Extract.—The effect of adrenal cortex extract treatment upon scald shock was studied in seven trials with 281 mice and three trials with 134 rats. The extract used was Cortin (Wilson), in a dose of 1 c.c. per 100 grams of body weight for both rats and mice. The extract was injected intraperitoneally one-half hour prior to scalding. Since the cortical extract is made up in saline, the control groups for the Cortin-treated animals received an equivalent volume of saline. The results of cortin treatment are shown in Fig. 1, *B.* It will be seen that adrenal cortical extract treatment had no therapeutic value.

THIAMINE

Thiamine has been reported to be therapeutically effective in hemorrhagic shock,[22] but this has been denied.[23] Further, thiamine does not possess therapeutic value in shock resulting from intestinal trauma.[23]

In our attempt to evaluate the effectiveness of thiamine in scald shock, eleven experiments, using a total of 475 mice, were performed. The mice in these experiments received 1 c.c. of saline, containing 10 mg. of thiamine chloride per 100 grams of body weight, by the intraperitoneal route, one-half hour prior to scalding. The control groups received saline in an equivalent amount.

The results, illustrated in Fig. 1, *C,* show that thiamine has slight or no significant therapeutic activity.

ASCORBIC ACID

Ungar[24] has reported that the administration of ascorbic acid in doses of 10 to 50 mg. per 100 grams of body weight is therapeutically

We therefore believed it necessary to ascertain whether or not agents which have been reported to possess therapeutic activity in shock are effective in the shock which follows scalding.

METHODS AND RESULTS

The scalding method utilized in these studies has been described previously in full detail.[1] Briefly, the method is as follows. Groups of twenty to thirty etherized rats or mice were submerged in scalding water of known temperature for definite periods of time. Rats weighing approximately 200 grams were scalded at 75° C. for fifteen seconds. The mice, weighing approximately 20 grams, were scalded at 65° C. for ten seconds. As in our previous work, the treated and control groups were derived from the same strain, with identical previous histories.

ADRENOCORTICAL HORMONES

Although it is definitely established that adrenalectomized animals have markedly lowered resistance to various types of trauma as compared with normal animals, and that treatment with adrenocortical hormones increases resistance toward normal,[2] the value of the adrenocortical hormones in the shock which occurs in intact, nonadrenalectomized animals has not been definitely ascertained.

Adrenal cortex extract has been reported to be useful in the treatment of toxic shock after intestinal obstruction[3] and the injection of the contents of a closed intestinal loop.[4, 5] Desoxycorticosterone produces no clear-cut effect in intestinal obstruction, although such treatment prevented the decline in plasma volume which is associated with this condition.[6] In the shock which follows intestinal trauma, it has been reported that cortical extract or corticosterones were effective, but that desoxycorticosterone was of no value.[7-9] Further, it has been observed that cortical extract therapy retards the decline in blood pressure which is associated with intestinal manipulation.[10] In hemorrhagic shock, it has been reported that cortical extract produces favorable results.[10] However, later observations in well-controlled experimentation have demonstrated the ineffectiveness of cortical hormone therapy in hemorrhagic shock.[11, 12] In the shock produced by venous occlusion of a hind leg, it has been reported that both cortical extract and desoxycorticosterone are effective when administered prophylactically.[13, 14] However, these results have not been confirmed.[15] It has been found that, although cortical extract was ineffective in preventing shock after venous occlusion, it did increase the efficacy of a salt infusion.[16]

Neither cortical extract nor desoxycorticosterone possesses therapeutic value in the shock induced in the dog by hind-leg trauma or by the release of tourniquets,[15] or in rats by tourniquet constriction.[17] In burn shock, there is evidence that cortical hormones are beneficial, for plasma electrolyte changes seem to be prevented,[18] and the efficacy of a plasma transfusion in increased.[19] However, further study of the latter point

injected either into the traumatized area or into a point distant from the injured area, proved therapeutically effective.

To ascertain the effect of nupercaine on scald shock, nupercaine was tested in five trials with 235 mice. The nupercaine was administered intramuscularly in a dose of 0.5 mg. per 100 grams of body weight, in a volume of 0.1 c.c. one-half hour after scalding. The nupercaine-treated mice were compared to controls which received no treatment.

The results are shown in Fig. 1, *E*, and illustrate the ineffectiveness of this treatment.

POSTTRAUMATIC CONVALESCENT SERUM

It has been shown that animals recovering from sublethal trauma due to a revolving wheel[26] or to temporary hind-leg ischemia[27] subsequently develop increased resistance and are able to withstand degrees of trauma that are usually fatal. Ungar[21] obtained similar results with the type of traumatic shock employed by him, but, in addition, he observed that the protective effect of previous trauma could be transferred from one animal to another and from one species to another by the injection of serum from traumatized animals.

To test the effect of postconvalescent burn serum, etherized rats were subjected to scalding, and serum was obtained from the rats which were still alive forty-eight hours after thermal injury. These sera were pooled and stored in the ice chest until ready for use. This posttraumatic burn serum from rats was tested for specific antiburn shock activity in five trials, using 240 mice as the test animals. The dose of serum, administered approximately thirty to sixty minutes after scalding, was 1 c.c. per 100 grams of body weight. The treated animals were compared to control groups which received no treatment. These results are given in Fig. 1, *F*, which shows that treatment with posttraumatic serum from burned rats was ineffective in preventing shock in mice subjected to scalding.

For comparative purposes, the results obtained in previous studies with 5 c.c. per 100 grams of body weight of physiologic saline, administered one-half hour after trauma, are given in Fig. 1, *G*.

SUMMARY

Our results demonstrate that, under the conditions of these experiments, neither desoxycorticosterone acetate, adrenal cortical extract, thiamine, ascorbic acid, nupercaine, nor posttraumatic convalescent serum from burned rats possessed significant antiburn shock activity.

Of the agents tested, all seemed definitely ineffective, with the possible exception of thiamine, which, although it did not decrease mortality, did somewhat increase the average survival. It will be seen that this beneficial effect was not consistent. Therefore, we conclude that, although thiamine may be slightly effective in burn shock, its activity

effective in traumatic shock. Similarly, it has been reported that ascorbic acid increases the resistance of dogs to acute hemorrhage.[25]

In our studies on the effect of ascorbic acid upon burn shock, six experiments, using a total of 297 mice, were performed. The dose of ascorbic acid was 50 mg. per 100 grams of body weight, and it was administered immediately after thermal trauma. In four trials, the ascorbic acid was injected intramuscularly in a volume of 0.1 c.c. of water. The ascorbic acid treated groups which received the substance by intramuscular injection were compared to groups which received no treatment; those that received ascorbic acid orally were compared to control groups which received 1 c.c. of water by mouth.

These data are shown in Fig. 1, *D*. The results indicate that ascorbic acid does not possess antiburn shock activity under the conditions of these experiments.

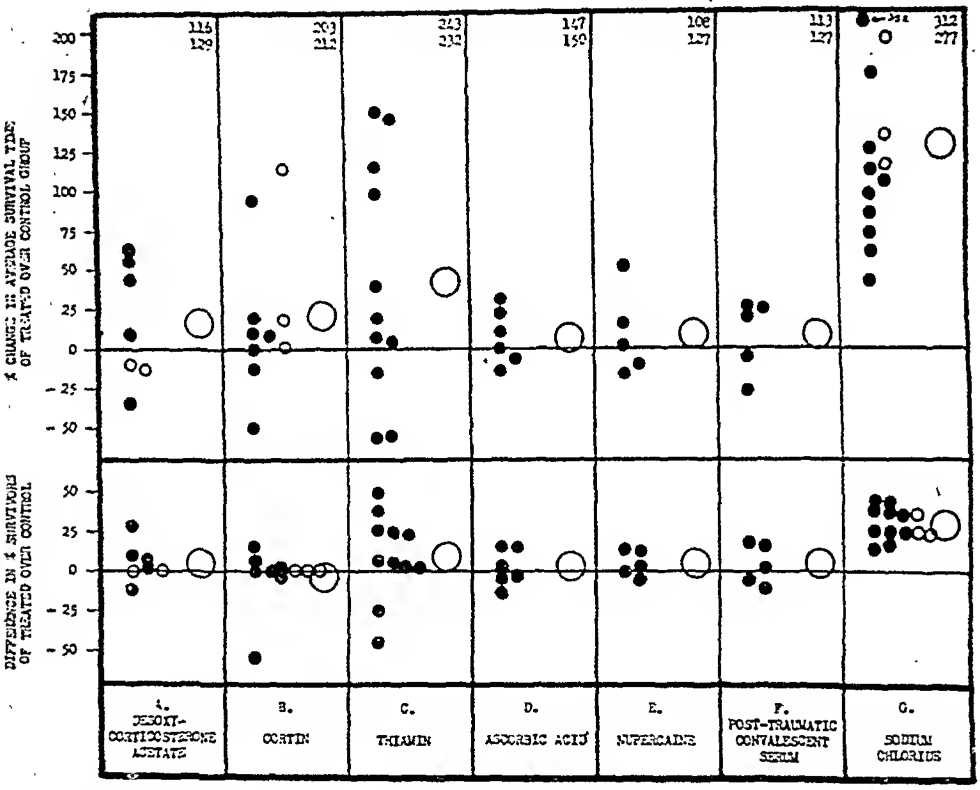

Fig. 1.—The effect of various therapeutic procedures on the response to thermal injury. Each dot and small circle represents the response of a group of at least twenty treated animals, as compared to an equivalent control group. The dots represent groups of mice, and the small circles, groups of rats. The large circles are means of the group responses. The figures in the upper right corner are the total number of treated animals over the total number of control animals.

NUPERCAINE

Stimulated by reports from Russia that the use of nupercaine for local anesthesia has resulted in a notable decrease in traumatic and surgical shock, Ungar[24] investigated the effects of local anesthetics upon experimental traumatic shock. He found that, although procaine was completely ineffective, nupercaine (4 mg. per kilogram of body weight),

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is small as compared to the results obtained with a highly effective agent such as large volumes of saline solution or pretreatment with liver extract.[1]

Examination of the results with all of the agents under investigation reveals that, in any single test, using twenty animals per group, apparently positive results are obtainable; but, when the tests are repeated, and the results are evaluated in composite form, it is evident that the so-called positive effects are due to variability of the method. Although we cannot state definitely that similar variations are encountered in evaluating antishock activity with other methods, it does appear possible that some of the conflicting results regarding various agents in shock may be explicable in terms of variability factors which were not taken into account.

It is not intended to imply that our observations necessarily apply to other forms of shock, produced by other procedures, for there is now evidence that the cause and treatment of various types of shock may be fundamentally dissimilar.[28, 29]

CONCLUSIONS

The therapeutic activity against shock due to a standardized scalding burn in rats and mice has been ascertained for the following substances: desoxycorticosterone acetate, adrenal cortical extract, thiamine, ascorbic acid, nupercaine, and posttraumatic convalescent serum. It was found that none of these agents possessed significant antiscald shock activity when tested on a sufficient number of animals under controlled conditions.

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EXPERIMENTS WITH SHORT-TERM INADEQUATE DIET

The effect of incomplete dietary regimes for two days upon resistance to scald shock was ascertained by comparing the survival after thermal injury of groups of mice fed several types of inadequate diets with control groups of mice fed the complete diet of Purina fox chow. All of these animals received water ad libitum. These experiments are summarized below.

Protein.—Casein (S.M.A. Corporation) was given ad libitum to five groups of mice, comprising 328 animals, for forty-eight hours. In addition, 1 c.c. of protein digest (Amigen, Mead Johnson), containing 10 per cent amino acids, was administered by stomach tube twenty-four and forty-eight hours prior to scalding. These mice lost approximately 15 per cent of their initial body weight.

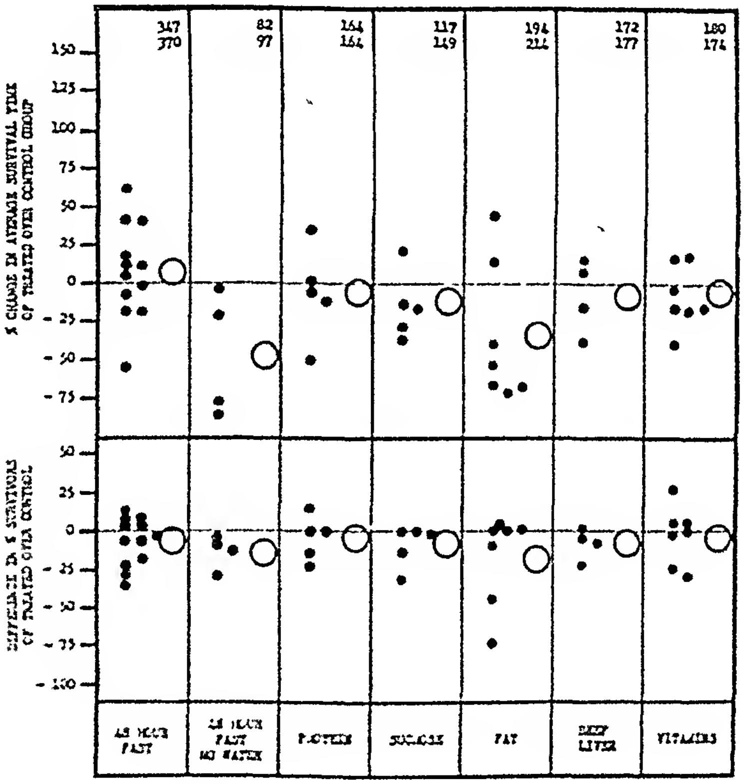

Fig. 1.—The effect of various short-term procedures on the response of mice to thermal injury. Each dot represents the response of a group of at least twenty treated mice, as compared to a control group containing an equivalent number of mice. The large circles are means of the group responses. The figures in the upper right corner are the total number of treated animals over the total number of control animals.

Sucrose.—Sucrose was given ad libitum to five groups of mice (total, 266) for forty-eight hours, during which time the average loss of body weight was approximately 10 per cent.

Fat.—A total of 408 mice were used. In three experiments, lard was fed ad libitum, and in four other experiments sesame oil was given by mouth in 0.5 to 1 c.c. doses twenty-four and forty-eight hours prior to scalding. The fat-fed animals lost from 15 to 20 per cent of their initial body weight. At the termination of the experiments, gross examination revealed that the livers of these animals were filled with fat.

EFFECT OF SHORT-TERM NUTRITIONAL STRESS UPON RESISTANCE TO SCALD SHOCK

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IN THE majority of instances, studies on experimental shock have been conducted with animals housed under protected laboratory conditions and receiving an adequate diet. However, shock as it occurs under combat conditions may be preceded by a wide variety of physiologic stresses, among which may be mentioned malnutrition and dehydration. The question arises as to whether preliminary subjection to short-term stress influences the ability of the organism to resist shock. In this report, studies are presented concerning the influence of short-term nutritional stress, such as fasting, water deprivation, and adequate dietary regimes upon resistance to the shock which follows thermal injury.

The details of the scalding method have been described in a previous report.[1] For the present experiments, groups of twenty or more mice of the same strain, weight range, and sex distribution were either deprived of food or given the particular diet for forty-eight hours prior to scalding. During this period, water was allowed ad libitum except for the water deprivation study. Purina fox chow was used as the complete diet for comparison with other diets. The mice, anesthetized with ether, were scalded at 65° C. for ten seconds. During the following forty-eight hours, no food or water was allowed. All mice alive at the end of this period were assigned an arbitrary survival time of forty-eight hours.

Forty-eight-Hour Fast.—To ascertain the influence of a forty-eight-hour fast upon resistance to scald shock, twelve experiments, comprising 717 mice, were performed, in which groups of fasted mice were anesthetized with ether, scalded, and compared to similarly treated groups which were fed fox chow ad libitum. Both groups had access to water up to the time of scalding. This forty-eight-hour fast decreased body weight approximately 15 to 17 per cent.

Forty-eight-Hour Fast, No Water.—The effect of water deprivation upon resistance to scald shock was studied in four experiments, using a total of 179 mice. Groups allowed neither food nor water for forty-eight hours were compared to groups allowed access to drinking water but no food. The dehydrated mice lost 17.5 to 20 per cent of their initial body weight, as compared to 15 to 17.5 per cent reduction for the mice which were allowed water but no food.

From the Straus Laboratory, Cedars of Lebanon Hospital, and the University of Southern California Medical School.

Aided by grants from the Blanche, May Selden Fund, the Martha Kirschner Haft Memorial Fund, F. Brice, Morton May, Walter Kirschner, and Mr. and Mrs. S. Marx.
Received for publication July 3, 1944.

UROLOGIC DISEASE AS A CAUSE OF HYPERTENSION

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THAT urologic disease or surgical conditions of the urinary tract, such as lithiasis, hydronephrosis, and pyelonephritis, may be causally related to hypertension in man seems possible.

The current clinical interest in this problem was aroused by the experimental studies of Goldblatt, in 1934, and of others in later years. Goldblatt, et al.,[1] recently pointed out that human hypertension associated with unilateral renal disease, such as chronic pyelonephritis or other conditions which disturb renal hemodynamics, has been recognized as an entity. The damage to intrarenal blood vessels resulting from such a disease is considered as favoring the secretion of a pressor substance, and hence as being a causative factor in the hyperpiesis. But others[2, 3] contend it has not been established that arterial and arteriolar changes always precede human hypertension. Whether vascular disease in the kidney is the cause, result, or both, of elevated blood pressure has not been definitely answered. Investigators have reported finding extensive histologic changes in renal vessels without hypertension, on the one hand, and hypertension without perceptible vascular changes, on the other.

Can definite evidence be found to substantiate the belief that urologic disease and high blood pressure are interrelated? Investigators have approached the problem along two avenues. Some have studied the incidence of hypertension in cases of known urologic disease, and others have reported the incidence of urologic disease among patients with hypertension.

The work of Weiss and Parker[4] has often been quoted to support the claim that pyelonephritis and hypertension are interrelated. These authors studied the kidneys of patients with pyelonephritis and high blood pressure, and believed their evidence indicated that hypertension in this condition depends on obliterative arteriolar lesions brought about by the infection. They admitted, however, that their method of selecting cases was such that the data were not suited to statistical analysis.

Barney and Suby[5] studied 305 cases of pyelonephritis and hydronephrosis on the Urological Service of the Massachusetts General Hospital, in 25 per cent of which there was hypertension. These authors employed a systolic blood pressure of 140 mm. Hg or more as the criterion for hypertension. Inasmuch as no control series was reported, the significance of their observations is not clear. Crabtree, Chaset, and Chaset,[6]

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Published with the permission of the Surgeon General of the United States Public Health Service.
Received for publication July 5, 1944.

Beef Liver.—Advantage was taken of the fact that mice fed nothing but minced beef liver for two days lost approximately 15 per cent of their initial weight. The effect of this diet of mixed composition, which does not maintain body weight, was studied in four experiments on 349 mice as regards resistance to scald shock.

Vitamins.—Seven groups of mice (total, 354) were given, by mouth, one drop of Haliver oil (Abbott) and 1 c.c. of a solution containing 2 mg. of thiamine chloride, 2 mg. of ascorbic acid, 0.4 mg. of nicotinic acid, 0.4 mg. of pyridoxine, 0.04 mg. of riboflavin, and 0.006 mg. of pantothenic acid twenty-four and forty-eight hours prior to scalding. Comparisons were made with mice which received 1 c.c. of water. Access to water was allowed in both cases. These groups lost approximately 15 to 20 per cent of their initial body weight.

Fig. 1 is a summary of the results obtained. Although there was a marked loss of body weight, it will be seen that neither a forty-eight-hour fast nor a previous short-term diet consisting solely of protein, carbohydrate, or fat had a significant influence on the mortality or the average survival time of mice subjected to thermal injury. Similarly, a diet of nothing but whole liver, which caused loss of weight, did not lower resistance.* Further, it was observed that large doses of a mixture of vitamins A and D, plus ascorbic acid, thiamine, and several members of the B complex group, did not modify the response to scald shock. The results with mice which were not allowed access to water for forty-eight hours show that there is a tendency toward lowered resistance, as evidenced by the decrease in the survival time after scalding.

It appears that, when dehydration is prevented, short periods of stress due to fasting or a poor nutritional regimen do not significantly reduce the resistance of mice subjected to thermal injury.

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*The amount of whole liver ingested in these feeding experiments was considerably less than the amounts of liver required to produce liver extracts with antiburn shock activity.[1]

tients was 38 years. Only 4.2 per cent had an elevated blood pressure, and this, they point out, is an incidence of hypertension of less than half that in the random sample of patients under 50 years of age at the Mayo Clinic. Our analysis of their data shows that the difference between 9.1 and 4.2 per cent, divided by its standard error, yields a value of 1.9, which is slightly lower than the level commonly accepted as a measure of significance.

Shure[10] found that the incidence of hypertension (150/95 or over) in a control group of 947 persons chosen at random was 34.9 per cent, as compared to 44.4 per cent of 290 patients with pyelonephritis. He concluded that in cases of bilateral pyelonephritis there appears to be a distinct increase in the incidence of hypertension. This difference seems to be statistically significant from a consideration of the standard error.

A compilation of the data presented in the papers just discussed would reveal that "hypertension" was present in 828, or 25 per cent, of 3,305 urologic cases; in contrast, 526, or 27 per cent, of 1,922 subjects serving as controls exhibited "hypertension." Obviously, these figures have little or no value because the same criteria were not utilized by the respective authors.

The incidence of urologic disease among hypertensive patients also has been studied by various investigators. Palmer and his co-workers[11] reported that 22 per cent of their 212 hypertensive patients had urinary tract disease, as diagnosed urographically. Pressures of 150/100 or over were regarded by these authors as being in the hypertensive range. Ratliff and Conger[14] found that, of 340 hypertensive patients who were not suspected of having urologic disease, 32, or 9.42 per cent, exhibited renal disease, as revealed by excretion and retrograde pyelographic study. They employed a level of 140/90 to divide hypertensive from normal subjects. In the course of routine examination, hypertension was found by Braasch[15] in 4,000 cases in which clinical evidence of a nonnephritic renal lesion was discovered in 100, or 2.5 per cent. This author refers to the so-called surgical kidney as "an etiologic factor of hypertension which has been definitely proved by clinical experience—."

Schroeder and Steele[16] studied 250 cases of essential hypertension, in 113 (45 per cent) of which there was some form of organic renal disease. They did not clearly state their criteria for hypertension. In another series of 100 cases of hypertension reported by Williams and Harrison,[17] 30 per cent of the patients had urologic disease. These workers employed a level of 150/100 in the segregation of hypertensives from normals. Wosika and Maher[18] reviewed the records of 574 hypertensive patients who were free from glomerulonephritis, and found that 101, or 16.8 per cent, had various surgical forms of urinary tract disease.

found that, of 150 consecutive patients with severe unilateral renal damage, 9.3 per cent showed an elevated blood pressure. They considered 150 mm. Hg, systolic, and 100 mm. Hg, diastolic, as hypertensive levels. These authors concluded that their patients with renal disease had a slightly lower average blood pressure than normal subjects. They employed for their control a series reported by another investigator. Abeshouse[7] observed that hypertension was present prior to operation in 17.3 per cent of 167 nephrectomized patients with unilateral renal disease (neoplasm, pyelonephritis, calculus, tuberculosis, etc.). Morlock and Horton[8] reported that 40 per cent of 335 patients with hypernephroma had hypertension. About 70 per cent were between the ages of 45 and 65 years. Among 124 patients with other types of renal tumors (sarcomas, squamous cell carcinomas, etc.), 46 per cent had hypertensive blood pressure levels. In this work they considered a systolic blood pressure of 140 mm. Hg or more as hypertensive. They found that no consistent alteration in blood pressure followed removal of the tumors.

Is it not possible for any comparably large group of persons to show a comparable incidence of hypertension, even though no renal disease is apparent or suspected? Of a random control group of 975 consecutive cases studied at the Mayo Clinic by Braasch and Jacobson,[9] 20 per cent were found to have hypertension (systolic, 145 mm. Hg, or diastolic, 90 mm. Hg, or more). Similarly, a study by Shure[10] revealed that 34.9 per cent of 947 persons chosen at random had blood pressures of 150/95 or more.

Of 1,684 patients with "surgical kidney" (adenocarcinoma, pyelonephritis, hydronephrosis, calculus, etc.), Braasch and his co-workers[11] found that 18.6 per cent had preoperative hypertension. In another study, limited to pyelonephritis, they[9] reported an incidence of hypertension of 26 per cent among 180 patients. Among persons 50 years of age or over, approximately the same proportion of both the pyelonephritic group and the control group exhibited high blood pressure, according to their definition, whereas, among the 119 test subjects under 50 years of age the incidence of hypertension associated with pyelonephritis was 16 per cent, as compared to 9.1 per cent of 606 members of the control group. As the authors point out, the incidence of hypertension was approximately twice as great in the younger pyelonephritic patients as in the younger control group. However, we have found that the standard error of the difference between these two values is 3.6, which makes the actual difference of doubtful statistical importance. In other words, "twice as much" in this instance is not impressive. Rather, it is a difference of 6.9 per cent (16 minus 9.1) that concerns us, and this deviation could well be the result of chance.

Braasch and Wood[12] more recently have reported on 70 cases of primary perinephritis or perinephritic abscess. The mean age of the pa-

sure. The erroneous conclusions which may follow such a classification in groups of older persons are apparent when one considers that systolic hypertension (high systolic, with normal or low diastolic, pressure) has its own distinct mechanism, and is caused by arteriosclerosis of the aorta and its larger branches. Clinicians are agreed that this form of elevation of blood pressure has no relation to essential or renal hypertension. One of us,[20] furthermore, has demonstrated that the incidence of systolic hypertension mounts sharply after the sixth decade. This consideration demands that no age discrepancies exist between test and control series. Without such careful control of the age factor, the employment of systolic pressure exclusively may lead to unjustified assumptions. There is strong evidence, moreover, that the diastolic pressure is a more reliable index than systolic pressure in the recognition of hypertensive disease.[20, 21]

In accordance with the foregoing concepts, we have studied a series of urologic and control cases in an attempt to add to the present knowledge concerning the relationship between arterial pressure and surgical diseases of the urinary tract.

MATERIAL

A group of 357 merchant seamen and coastguardmen served as test subjects. The three chief conditions, singly or in combination, for which they were hospitalized were nephrolithiasis or ureterolithiasis, hydronephrosis, and prostatic hypertrophy. A smaller number of the men were suffering from pyelitis, pyelonephritis, bladder stone, ureteral stricture, and pyonephrosis. All diagnoses were confirmed by roentgenographic, cystoscopic, or operative procedures. Of the patients with prostatic disease approximately 15 per cent had acute retention when they were admitted to the hospital. The average age of the 357 patients was 44.3 years.

Serving as controls were 654 patients selected at random, all of whom were merchant seamen or coastguardmen of the same habits and background as the urologic patients, but were hospitalized for other reasons. Their average age was 46.4 years. The difference between the average age of the control and test groups was not statistically significant; T* was 1.9.

RESULTS

Study of Table I will show that the urologic patients as a whole, or when considered by age groups, had no higher average blood pressure than the control subjects. In fact, the data reveal a slightly, but significantly, higher average systolic pressure in the majority of the con-

*T is the difference divided by the standard error of that difference, and was calculated, when applied to means, by Formula A, and by Formula B when applied to percentages. A T level of 2.5 or more was adopted as a measure of statistical significance.

$$\text{(A)}\quad \frac{M_1 - M_2}{\sqrt{\frac{S.D._1^2}{n_1} + \frac{S.D._2^2}{n_2}}} \qquad\qquad \text{(B)}\quad \frac{P_1 - P_2}{\sqrt{\frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}}}$$

where $M_1 - M_2$ is the difference between means; S.D., standard error; n, number of cases; $p_1 - p_2$, difference between proportions; p, percentage in one sample having the characteristic; q, percentage in same sample not having the characteristic.

Wosika, Jung, and Maher[19] reported that, in a large series of postmortem protocols, 27.4 per cent of a group with normal blood pressure, and 40 per cent of a hypertensive group, had urologic disease. They applied the chi square test to their data and considered that the difference between the groups had statistical significance. These authors conclude, "one may safely infer that a patient with hypertension is more likely to have urologic disease than is a patient without hypertension." Although these results appear impressive, it should be emphasized that what Wosika and his associates term "hypertension" is actually elevation of the systolic blood pressure (140 mm. Hg or more). In their opinion, the systolic level appears to be an adequate criterion for hypertension. They state further that, "including the diastolic pressure . . . is not only impractical clinically, but it obscures the logic, complicates the mathematics, and attenuates the statistical analysis." Because of these remarks and for reasons to be discussed we are not convinced that the results of their study are valid.

If one attempts to compile the data supplied by these seven papers it would appear that, of a total of 6,044 so-called hypertensive patients, 650, or 10.7 per cent, exhibited evidence of urologic disease. In the nonhypertensive control group collected by Wosika and his associates, however, 167 of 611 subjects, or 27.4 per cent, proved to have urologic conditions. Judging from these collected figures, the incidence of urologic disease in a large group of "hypertensive" patients appears no greater (if not actually less) than the incidence in a group of nonhypertensive patients. Here again, such compiled data must be considered with caution because the blood pressure criteria, as well as control methods, varied among the different investigators. These diverse observations of independent workers who report an incidence of urologic disease among hypertensive subjects ranging from 2.5 to 45 per cent clearly indicate that the problem has not yet been solved.

In the studies we have briefly reviewed we noted that in some instances investigators failed to employ a control series for comparison. Consequently, evaluation of their results is difficult. Other workers have made little or no attempt to interpret statistically the results of their studies. Unless the reliability of a difference between two sets of figures has been estimated, inferences cannot be safely drawn from that difference. Without the employment of even some simple probability test, we may err by building arguments on a foundation which is insecure because of improper sampling. But even prior to the application of statistical methods, it must be ascertained that the basic material is free from fault.

A great source of confusion is derived from the diversity of opinion regarding the definition of hypertension. Some authors have used only the systolic blood pressure as a criterion of hypertension. Consequently, the same significance was assigned to all elevations of systolic blood pressure, regardless of the accompanying level of diastolic pres-

Table 1

Average Systolic and Diastolic Blood Pressures Among Urologic and Control Cases

Age (yrs.)	Total Number of Cases: Urologic	Total Number of Cases: Control	Average Systolic Blood Pressure: Urologic (mm.Hg)	Average Systolic Blood Pressure: Control (mm.Hg)	T*	Average Diastolic Blood Pressure: Urologic (mm.Hg)	Average Diastolic Blood Pressure: Control (mm.Hg)	T*
10 to 19	7	38	113.56	125.78	a	70.85	82.1	a
20 to 29	68	160	123.52	120.25	0.8	78.38	81.2	1.9
30 to 39	79	86	122.72	130.24	3.4	80.32	83.3	1.7
40 to 49	75	85	127.54	134.3	2.2	82.6	86.1	2.2
50 to 59	58	63	139.82	137.8	0.5	87.94	85.31	1.2
60 to 69	57	117	146.23	153.2	2.3	90.09	89.1	0.4
70 to 79	13	104	142.0	160.0	a	80.84	88.5	a
80 to 89	0	1	–	(125)	–	–	(75)	–
10 to 49	229	369	124.84 ± 1.03b	129.16 ± 0.77	3.2	80.34 ± 0.67	82.32 ± 0.64	2.1
50 to 89	128	289	142.6 ± 2.10	152.16 ± 0.98	3.8	86.46 ± 1.21	86.8 ± 0.96	0.2
10 to 89	357	645	131.9 ± 1.13	139.8 ± 0.82	5.6	82.9 ± 0.64	85.09 ± 0.54	2.5

a = Too few cases for statistical comparison.
b = These ± values represent standard errors.
*See footnote on page 518.

trol groups. The urologic patients had average systolic blood pressures which were higher than the controls only in the 20 to 29 and 50 to 59 age ranges, but these differences were not statistically significant, as evidenced by T values of 0.8 and 0.5, respectively. Analysis of the diastolic blood pressures similarly indicates no correlation between urologic disease and elevated levels.

Table II shows the relation of age to the incidence of various blood pressure levels in control and urologic groups. All pressures below 145/95 were classified as normal; systolic pressures of 145 or above, with diastolic pressures under 95, were regarded as indicative of systolic hypertension; when the diastolic pressure was 95 or above, diastolic hypertension was said to be present.

From the data in Table II it is apparent that the minor differences between test and control groups can readily be explained on chance occurrence. The influence of age upon arterial pressure is clearly demonstrated by Tables I and II. With advance in age there is not only a rise in average systolic and diastolic blood pressure in both urologic and control groups, but also a concomitant increase in the incidence of systolic hypertension and of diastolic hypertension. Conversely, there is a diminishing frequency of normal blood pressure with advancing years. These trends are made more evident by the comparison between "younger" (10 to 49 years) and "older" (50 to 89 years) persons. That the differences between these two major groups are significant is demonstrated by T values ranging from 3.4 to 17.9.

When the urologic patients are divided into the three main classifications, hydronephrosis, kidney and ureteral lithiasis, and prostatic hypertrophy, and their average blood pressures are compared with controls of corresponding age, the results again indicate that the differences between the means are likely due to chance (Table III). The pyelonephritis, bladder stone, pyonephrosis, and pyelitis groups were too small to be listed in Table III for statistical comparison. A discrepancy will be noted between the total number of cases in the three groups of urologic cases in this table, as compared with the test group described in Tables I and II. This is explained by the fact that some of the patients had a combination of these urologic conditions.

DISCUSSION

To ascertain whether urologic hypertension exists as an entity, we have compared a group of patients who had surgical conditions of the urinary tract with a nonurologic series. In this study we attempted to control such factors as age, sex, and occupation in both groups. We already have pointed out that the use of systolic blood pressure as the only criterion for dividing normal from hypertensive levels may be a serious source of error, in view of the fact that a high incidence of systolic hypertension normally occurs in older persons (Table II). Hence, we have broken down our data according to age and average systolic and diastolic pressure, and according to the percentage incidence

Bicknell,[22] in discussing the incidence of hypertension in patients with "surgical" kidneys, considered that the age factor appears to have more influence than any other. He admitted, for instance, that hypertension is common in patients with hypernephroma, but, on analysis, observed that the majority of such patients are in the sixth decade or beyond.

Hines and Sander[23] compared the blood pressure on the original examination with the subsequent development of hypertension (160/100 or more) ten and twenty years later in a series of urologic patients and in a control group. They reported a striking coincidence of data in the two series. When the age factor was considered, no significant difference could be found in the incidence of subsequent hypertension. They concluded that the latter is more closely related to the height of the blood pressure on the original examination than to the extent of the renal lesion or the known duration of the urologic disease, and that their data seem to cast doubt on the importance of renal disease in producing hypertension.

Because of the supposed relationship between urologic disease and hypertension, nephrectomy has been recommended by some workers for the relief of elevated blood pressure of patients with unilateral renal lesions. Has it been demonstrated that the removal of the affected kidney in such cases is followed by a reduction in blood pressure? If temporary decreases in the arterial pressure have been observed, has cognizance been taken of the fact that any surgical procedure or even prolonged bed rest without surgical intervention may cause a reduction in blood pressure? Sensenbach[24] recently reviewed the literature on nephrectomy in the treatment of hypertension, and found that, in the 75 cases he collected, only 6.6 per cent of the patients had normal blood pressure two years or more after operation; about one-third had a fall in blood pressure, but had been followed less than two years at the time their cases were reported; one-third showed a reduction, but remained hypertensive, and, in one-third, the blood pressure was unaltered or higher. On the other hand, the observations of Goldblatt[25] and Braasch,[26] in several cases followed over a period of years, seem to offer strong evidence that a causative relationship does occasionally exist. That such relationship must indeed be uncommon is suggested by our failure to establish a correlation between urologic disease and hypertension in this study.

SUMMARY

1. A review of the literature has demonstrated that there is no conclusive proof that urologic disease frequently causes hypertension.

2. Criticisms of methods employed by some investigators in the study of this problem include lack of control series, omission of statistical evaluation of the results, and the use of systolic blood pressure alone in defining "hypertension."

TABLE II

PERCENTAGE INCIDENCE OF NORMAL BLOOD PRESSURE, SYSTOLIC HYPERTENSION, AND DIASTOLIC HYPERTENSION AMONG UROLOGIC AND CONTROL SUBJECTS

AGE (YRS.)	NORMAL BLOOD PRESSURE UROLOGIC (%)	NORMAL BLOOD PRESSURE CONTROL (%)	T*	SYSTOLIC HYPERTENSION UROLOGIC (%)	SYSTOLIC HYPERTENSION CONTROL (%)	T*	DIASTOLIC HYPERTENSION UROLOGIC (%)	DIASTOLIC HYPERTENSION CONTROL (%)	T*
10 to 19	100	100	–	0	0	–	0	0	–
20 to 29	91.1	94.3	0.8	2.9	2.5	1.0	5.9	3.12	0.3
30 to 39	93.7	90.2	0.8	2.5	4.6	0.7	3.8	5.81	0.6
40 to 49	85.3	84.7	0.1	8.0	5.8	0.5	6.6	11.76	1.1
50 to 59	65.5	74.6	1.1	18.9	14.2	0.8	15.5	11.11	0.7
60 to 69	46.6	42.7	0.5	31.5	33.3	0.2	22.7	23.93	0.1
70 to 79	61.6	31.7	a	30.7	42.3	a	7.6	25.00	a
80 to 89	–	(1 case)	–	0	0	–	0	0	–
10 to 49	90.3	91.0	0.2	4.36	3.52	0.6	5.24	5.41	0.1
50 to 89	56.2	45.9	1.9	25.78	32.28	1.3	17.96	21.75	0.92
10 to 89	*78.1*	*71.46*	*2.3*	*12.04*	*16.05*	*1.8*	*9.8*	*12.53*	*1.3*

Normal blood pressure, 144/94 or below.
Systolic hypertension, 145 mm. Hg systolic or over, with diastolic 94 mm. Hg or below.
Diastolic hypertension, 95 mm. Hg diastolic or over.
a = Too few cases for statistical analysis.
*See footnote on page 518.

of normal blood pressure, systolic hypertension, and diastolic hypertension. We were unable to demonstrate an association between urologic disease and hypertension. We found, as others previously have observed, that the age factor has a definite influence on systolic and diastolic blood pressure. Our data show that increments in arterial pressure occur with age in our test and control groups. The percentage incidence of systolic hypertension in the younger urologic and control series was 4.3 and 3.5 per cent, respectively, as compared with 25.7 and 32.2 per cent, respectively, in the older subjects (50 years and over). The percentage incidence of diastolic hypertension in the younger urologic and control series was 5.2 and 5.4 per cent, respectively, in comparison to 17.9 and 21.7 per cent in the older subjects. Of the entire test group, 12 per cent had systolic hypertension, and 9.8 per cent, diastolic hypertension. The respective values in the control series were 16 and 12.5 per cent.

TABLE III

AVERAGE SYSTOLIC AND DIASTOLIC BLOOD PRESSURE OF PATIENTS WITH HYDRONEPHROSIS, PROSTATIC HYPERTROPHY, AND RENAL AND URETERAL LITHIASIS, COMPARED WITH CONTROL SUBJECTS OF THE SAME AGE

	NUMBER OF CASES	AVERAGE AGE (YRS.)	AVERAGE SYSTOLIC BLOOD PRESSURE (MM. HG)	T*	AVERAGE DIASTOLIC BLOOD PRESSURE (MM. HG)	T*
Controls	86	30 to 39 (35)	130.24		83.3	
Hydronephrosis	122	38.15	126.0	2.0	81.53	0.5
Lithiasis	156	39.21	129.36	0.5	82.18	0.8
Controls	63	50 to 59 (55)	137.81		85.31	
Prostatic Hypertrophy	122	56.06	142.06	1.2	86.97	0.9

*See footnote on page 518.

A MORPHOLOGIC STUDY OF THE CARDIAC CONDUCTION SYSTEM

Part IV: The Anatomy of the Upper Part of the Ventricular Septum in Man

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THE observers who describe the atrioventricular conduction system of the heart locate its principal parts in the upper part of the ventricular septum and the immediately adjoining right atrial wall. In order to obtain a conception of the anatomy of this region, we have studied, grossly and microscopically, more than forty human hearts. Our observations follow.

The atrial muscles terminate in the atrioventricular fibrous rings. These rings separate the upper and lower cardiac chambers and form the fibrous bases for the atrioventricular valves. The posterior mesial segment of the left atrioventricular fibrous ring swings forward and to the right, terminating in the central fibrous body (trigonum fibrosum) at the level of the posterior aortic wall. The analogous segment of the right ring runs across the upper right ventricular septum, fusing with the septum membranaceum. From the base of the mesial cusp of the tricuspid valve, strong fibrous bands (fila coronaria) extend to the central fibrous body and to the aortic ring in front of it. The central fibrous body, a stout post of connective tissue joining the atrial and ventricular septa, appears to be formed by fusion of the substance of the entire mesial segment of the left ring with a portion of the mesial segment of the right. The anterior portion of the central fibrous body fuses with the aortic ring, which forms the septal base of the aorta and joins the septum membranaceum. The portion of the aortic ring just anterior to the central fibrous body splits into two sheaths, which form a gabled roof for the central part of the muscular ventricular septum. The septal base of the aorta, the septum membranaceum, the fibrous base of the mesial tricuspid, and the endocardium covering the upper part of the septum can be removed by meticulous dissection, which makes plainly discernible the architecture of the upper part of the interventricular septum.

On the left side of the septum, posteriorly, the subendocardial muscle fasciculi radiate toward the central fibrous body where they are attached. Anteriorly, near the upper posterior edge of the septum membranaceum,

Aided by grants from the American Medical Association and the Iowa Methodist Hospital.

Received for publication Feb. 17, 1945.

3. Our observations on 357 urologic cases and 654 control subjects tend to invalidate the impression that surgical conditions of the urinary tract as a general group are causally related to elevation of the blood pressure, although the causal relationship in individual cases cannot be denied.

The authors wish to acknowledge their appreciation to Dr. Charles Ferguson for use of urologic case records.

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portion. The supravalvular segment, which is from 1 to 2 cm. long, is slightly oval, and has a diameter of 1 to 2 millimeters. After it emerges from the canal in the central fibrous body, it lies in intimate contact with the other fasciculi of the septum. (Therefore, it seems absurd to believe that the wave of excitation could be insulated in its few muscle cells. We are also unable to understand why this bundle could not be seen with the naked eye.) The infravalvular portion,

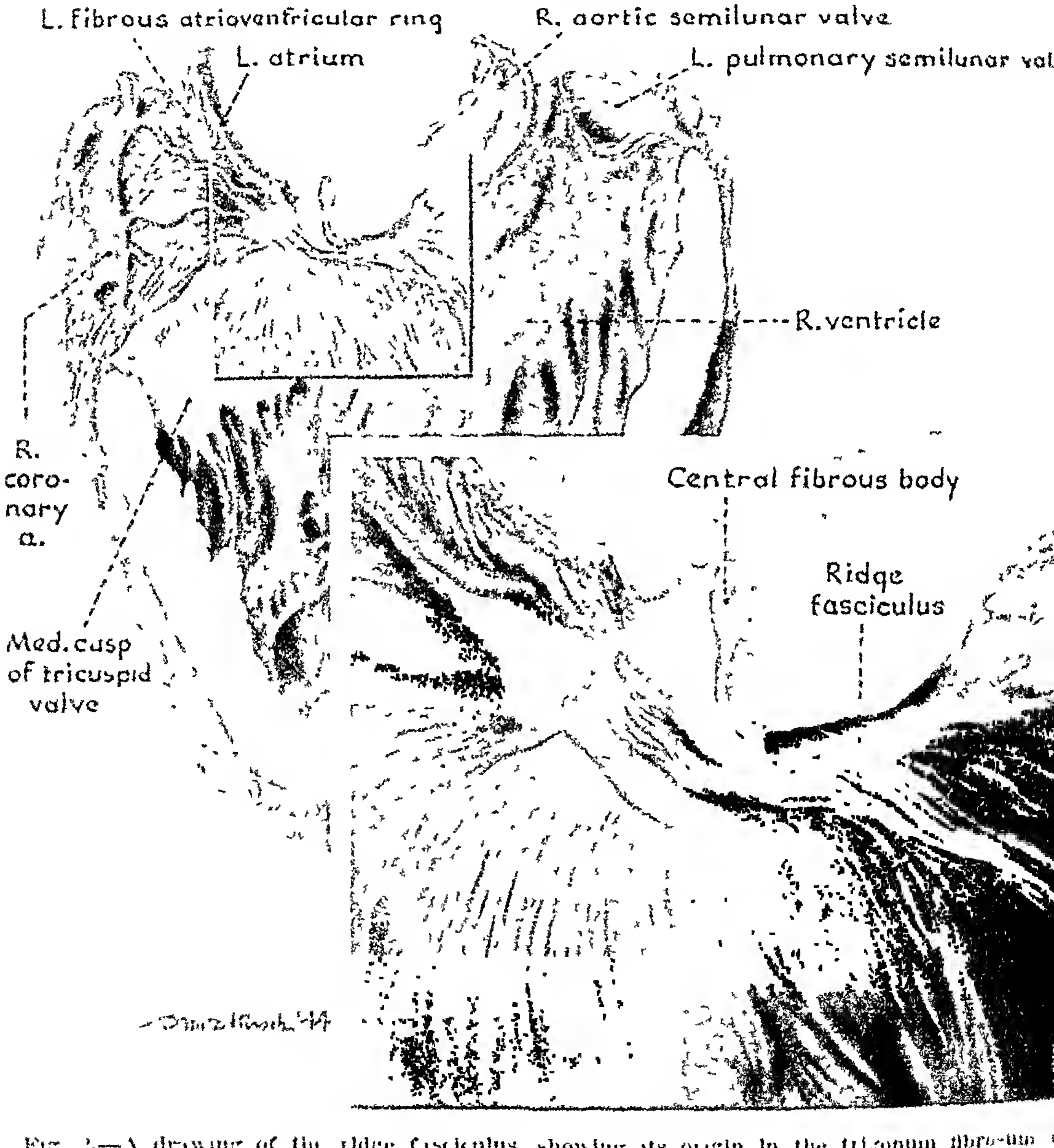


Fig. 2.—A drawing of the ridge fasciculus, showing its origin in the trigonum fibrosum its relation to the septal musculature, also the ramus septi fibrosi (artery) to the node.

which is often cylindrical, measures about 1 mm. in diameter. *It does* not possess a special connective tissue sheath. If there is a groove running from the valvular incisure toward the apex, the infravalvular part of the fasciculus lies on the posterior margin of that groove and is often superficial. In hearts in which it is superficial it can be readily fol-

a similar grouping of superficial fasciculi usually occurs. Near the aortic ring these fasciculi often form a lump from which muscle fibers stream toward the papillary muscles and the apex. Wilhelm His, Jr.,[1] pictures and describes them as the atrioventricular bundle (Fig. 1). We have not observed any muscular connection between these fibers and the ridge fasciculus, the description of which follows. Other careful observers have failed to find, in carnivora, a bifurcation of the fasciculus described by Tawara as the stem of the His bundle. Mahaim depicts the left branch of the His bundle as having four distinct roots originating at separate points of the upper ventricular septum (see Part III).

On the right side of the septum all of the subendocardial muscle fibers behind the fissure, betwen the mesial and anterior cusps of the tricuspid valve, radiate toward the central fibrous body where they are attached (Fig. 2). The most posterior fasciculus runs forward parallel to the ridge of the septum and is attached to the central fibrous body. Similarly, the most anterior fasciculus runs backward; it, also, is attached to the central fibrous body.

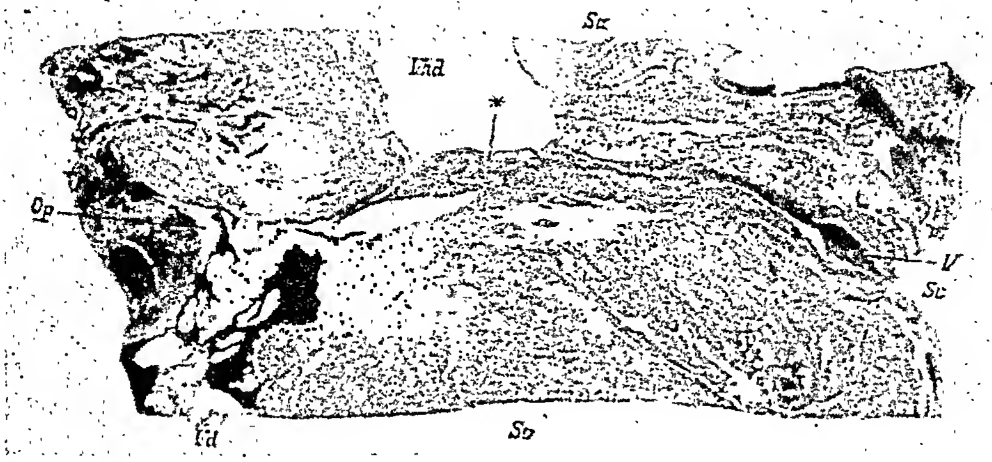


Fig. 1.—Atrioventricular bundle (Wilhelm His, Jr.). Sagittal section of the atrioventricular border of the heart of a newborn human (×7.5). The ventricular septum is cut longitudinally, the auricular septum, only partly so. *Vhd*, cavity of the right atrium; *Vd*, cavity of the right ventricle; *Sv*, ventricular septum; *Sa*, atrial septum; *Sc*, coronary groove; *V*, coronary vein; *Op*, pulmonary ostium; and *, atrioventricular bundle.

This most anterior bundle we designate the ridge fasciculus. It has been much studied as the main stem and right branch of the His bundle. This insignificant bundle is not always present. We have found it in over two-thirds of the hearts studied. It, like the rest of the subendocardial muscle fasciculi, varies in size, direction, and relation to other muscle fibers. Its color is, as a rule, lighter than the surrounding, more deeply imbedded, bundles. It originates deep in the ventricular portion of the central fibrous body, from 2 to 3 mm. below the insertion of the atrial muscle fibers (Fig. 2). It runs forward for a short distance in a fibrous canal in the anterior part of the central fibrous body (Fig. 7, Part II) and continues forward and downward toward the right septal papillary muscle. It has a supravalvular and an infravalvular

with connective tissue, poor in cells. Through the node, or to the side of it, runs the "artery to the node." We have not found such a node in the posterior *atrial* wall in any of the mammals that we have examined. The ramus septi fibrosi (Haas) runs in the atrioventricular groove, and, so far as our observations go, never in the atrial wall. We[2] have described the node of Tawara in ungulates. In these animals it is a part of the musculature of the upper ventricular septum. From it the muscular part of the "Purkinje" bundle arises. The node lies behind the central fibrous body. Its muscle cells change abruptly to the characteristic Purkinje fibers at the place where the nerve trunks enter the bundle.

It has already been stated that in human hearts the ridge fasciculus originates deep in the ventricular part of the central fibrous body. In order to study the origin and the environs of this fasciculus histologically, we removed the posterior atrial wall by severing the central fibrous body below the attachment of the atrial muscle fibers. Blocks were cut from this part of the upper ventricular septum. Posteriorly, the blocks terminated a few millimeters behind the "nodal artery" where it enters the septum; anteriorly, they extended several millimeters in front of the canal in the central fibrous body. Microscopic sections parallel to the muscle fibers of the ridge fasciculus were cut to include the beginning of the fasciculus, in front, and the "artery to the node," behind. The histologic structure of the origin of the ridge fasciculus is shown in Fig. 3, *A*. It is obvious that the appearance of a reticulum in this region is due to the intertwining of ventricular muscle fibers at their attachment to the central fibrous body, and that the muscle fibers are a part of the ventricular septum.

Tandler,[3] Spalteholz,[4] Gross,[5] Mahaim,[6] and, more recently, Lascano[7] have described a special arterial supply to the His-Tawara system in man. On the basis of the theory that the arteries which supply the system are "end arteries," the lesions that are thought to cause block have been assumed to be due to obstruction of the arterial twigs which supply the system. The artery to the node (ramus septi fibrosi, Haas) is said to supply the node and the stem of the His bundle. Gross describes a rather large septal branch of the anterior ramus descendens as the ramus limbi dextri. Mahaim states that the left branch has a double blood supply, that the anterior limb is supplied by a branch from the anterior descending artery and the posterior limb by a branch from the posterior descending artery. The coronary arteries, which supply the septum, have been made visible by means of opaque media by Spalteholz, Gross, and Lascano. The Argentine investigator states: "The arteries entrusted with the blood supply to the node, the bundle of His and its branches, anastomose with one another and do so with the nutrient arteries of the non-specific myocardium—therefore, . . . these arteries are merely the main arteries, not terminal vessels, to the abovenamed node, bundle, and its branches."

lowed to the base of the papillary muscle. When it lies deeper, it can also be followed. In both cases it can be followed in serial sections.

The histologic structure of the ridge fasciculus, evident in Figs. 3 and 4, is also clearly depicted in Mahaim's microphotographs. We have stated previously that the structure of the fasciculus is identical with neighboring muscle bundles and that we have not encountered blood vessels larger than arterioles in the fasciculus. Nerve fibrils were not detected by the histologic technique which we employed.

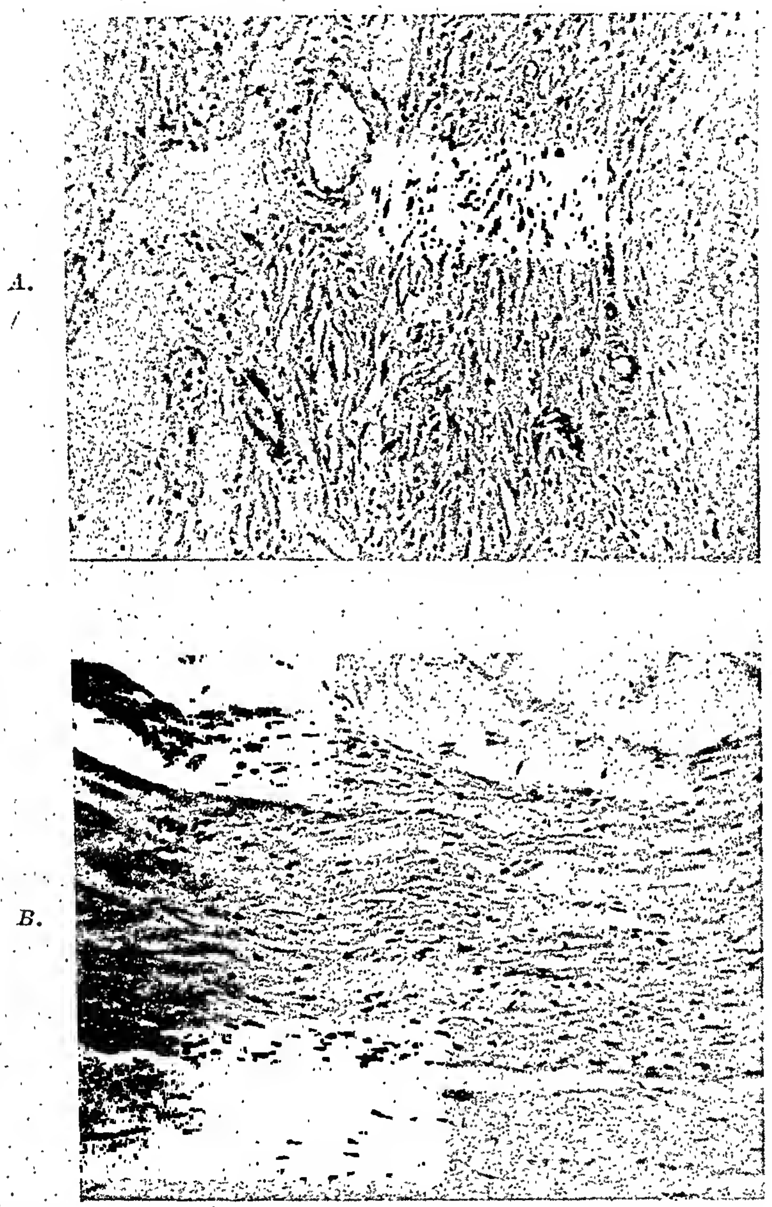


Fig. 3.—Microscopic structure of the supravalvular part of the ridge fasciculus. Longitudinal sections (×75). *A*, "Nodal" region. *B*, "Stem" region.

According to the orthodox view, this ridge fasciculus originates in the atrioventricular node, located in the posterior atrial wall, but in none of the hearts that we studied did we find it entering atrial myocardium. The atrioventricular node is described by Tawara as a reticulum of slender, indistinctly striated muscle fibers from which the His bundle originates. The interstices of the nodal reticulum are filled

is the largest septal branch given off from the anterior ramus descendens. It often measures 2 mm. in diameter. It plunges directly into the muscular septum and, by ordinary dissection, can be followed for only a short distance. We are not certain which of the many small branches given off from the anterior and posterior rami descendens are the ones which Mahaim considers the arteries to the anterior and posterior limbs of the left branch of the His bundle.

The observers who describe a special blood supply for the atrioventricular bundle offer no evidence that the arterial twigs which they describe actually supply the "conducting bundle," or that they supply *only* that fasciculus. Their illustrations shed no light on the problem. It seems absurd to us to claim that such *large* arteries have the sole function of supplying the *tiny* ridge fasciculus. As previously stated, no arteries larger than arterioles have been found by us or others in microscopic sections of this bundle. We hold that the special-blood-supply theory is as much a myth as is the concept of the conducting bundle itself.

In the mammalian hearts that we examined we found no valid anatomic evidence to support the myogenic theory of cardiac conduction. It seemed natural, therefore, to search for morphologic evidence for the neurogenic concept. This theory assumes that the cardiac impulse originates in the bodies of motor neurons and is transmitted to the myocardial elements through their axis cylinders. Obviously the activating neurons must be located within the cor itself, because hearts of the most highly developed mammals are capable of rhythmic contraction after all nerve connections with the rest of the body are severed. It is anatomically impossible for a single cardiac chamber to function independently, for the muscle bands which constitute the atrial myocardium run continuously from one atrium to the other, and all the spiral muscles of the ventricles, with one exception, are common to the lower chambers. Clinical and experimental observations clearly indicate that the paired ventricles and paired atria are capable of independent rhythmic contraction. Therefore, if the neurogenic theory is correct, there must exist in the heart at least one atrial and one ventricular pacemaker. Since it has been established that in adult animals cardiac contraction begins in or near the sulcus terminalis, it is logical to search for a nerve pacemaker in this region; and because there is good electrocardiographic evidence that ventricular activation begins in the upper part of the interventricular septum, a ventricular pacemaker may be found in this locality. These theoretic considerations lead to a discussion of the anatomy and physiology of the intrinsic nerve tissue of the heart.

The nerve tissue of the heart has been studied by many investigators. We have reviewed the observations of the following more recent students of this phase of cardiac anatomy: Dogiel,[8] 1899; Müller,[9] 1924; Perman,[10] 1924; Fukutake,[11] 1925; and Woollard,[12] 1926. Their observations are summarized briefly in the following paragraphs.

In a special study of the septal coronary arteries of ten human hearts, we made the following observations:

The posterior septal part of the atrioventricular groove is deep (2 to 3 cm. in normal hearts). It terminates anteriorly in the central fibrous body and the aortic ring. The "artery to the node," which runs in this groove, is one of several septal twigs of the coronary artery which gives off the posterior descending branch. In some hearts this

A.

B.

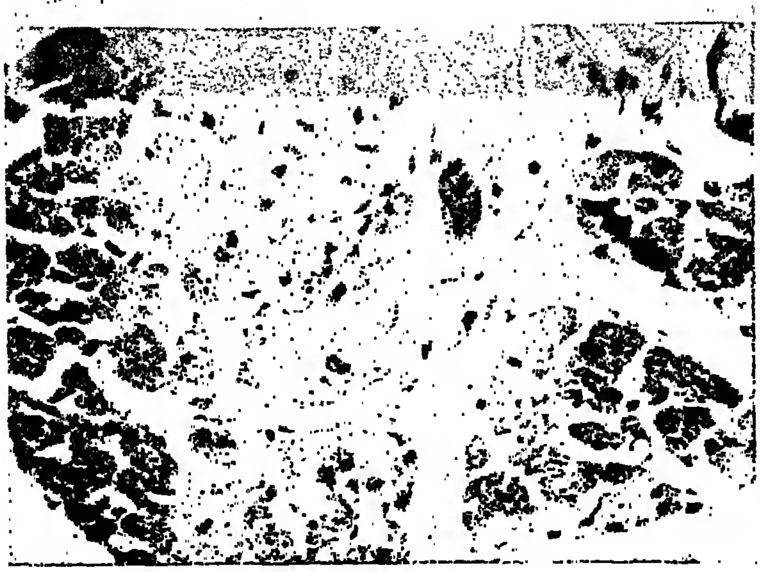


Fig. 1.—Microscopic structure of the infravalvular part of the ridge fasciculus. Cross section. The ridge fasciculus is seen at the extreme right. *A*, Showing relation to other myocardial fibers. *B*, Higher magnification of *A*.

twig does not reach the central fibrous body, but enters the septum some distance behind it (Fig. 2). The diameter of the vessel varies from 1 to 2 millimeters. It lies in the loose, adipose tissue which fills the groove and, as a rule, divides into two or more branches which enter the septal musculature near the central fibrous body. The artery which Gross named "the artery to the right branch of the His bundle"

of the so-called cardiac conduction system, we were astonished at the abundance of nerve cells encountered. The nerve cells seemed more numerous in the right atrium than in the left.

In the sulcus terminalis two types of ganglia were found. The larger groups, consisting of large cells, were closely associated with the entering vagi; the smaller, made up of smaller cells, were found some distance from the nerves. These two types of nerve cells were found in every species examined. Nerve cells were numerous around the inferior vena

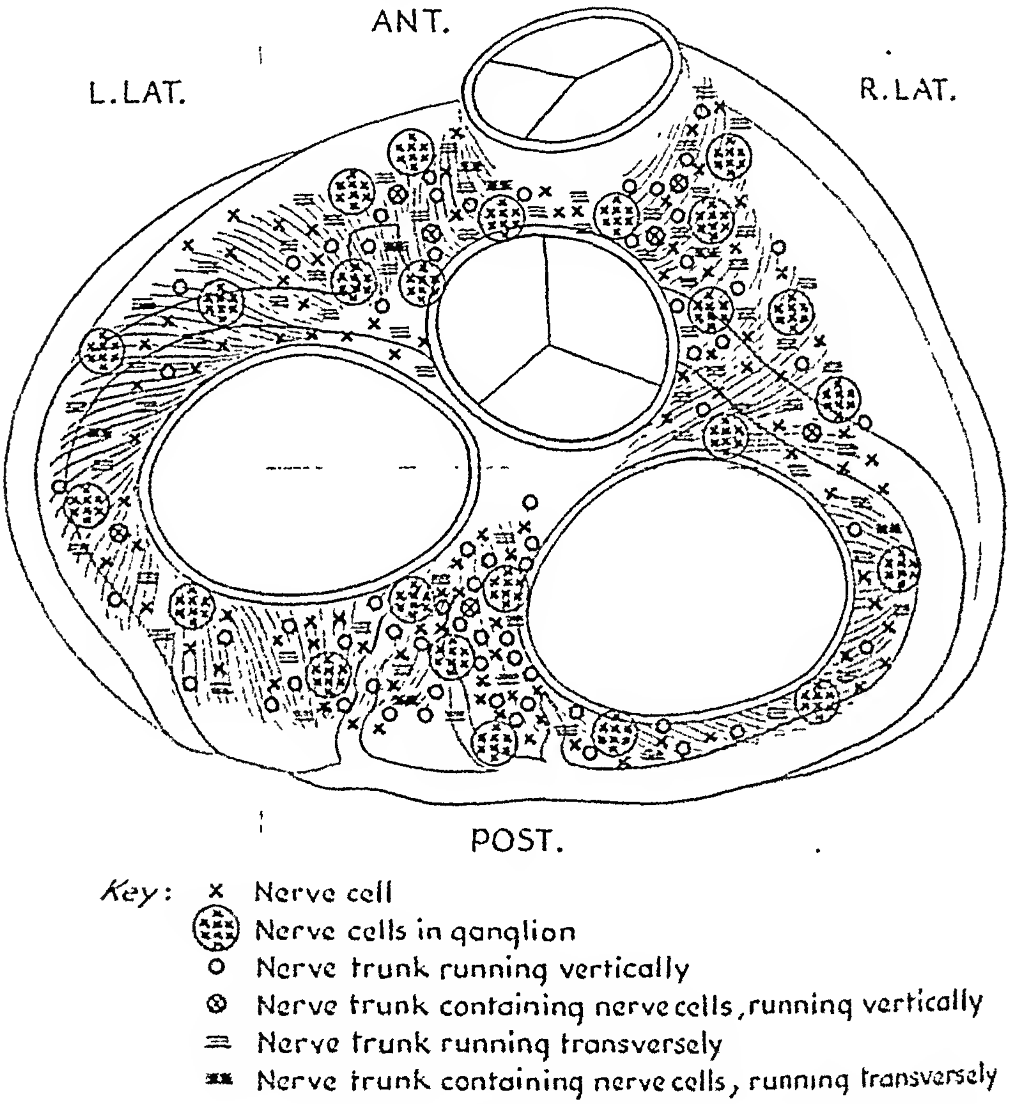


Fig. 5.—A schematic drawing showing the distribution of nerve cells in the atrioventricular groove.

cava. In the horse, we encountered a large collection of nerve cells in the anterior wall of the right atrium, slightly to the left of the opening of the inferior vena cava. In all the ungulates studied, large collections of nerve cells occurred just behind the central fibrous body, and the nerve fibers from these cells constituted more than half of the substance of the Purkinje bundle. Nerve cells were also found in the right and the left branches of this bundle.

The ganglia of Remak, Bidders, and Ludwig are but a small part of the extensive nerve tissue found in the hearts of higher animals. The intrinsic nerve elements of the heart consist of nerve cells, nerve trunks, and plexuses of nerve fibrils. The nerve cells occur underneath the pericardium. They are exceedingly numerous in the atria, and are also numerous in the atrioventricular sulcus, but are rarely present in the ventricles. However, Dogiel found ganglion cells in the frog even at the apex, and Woollard found nerve cells in the interventricular furrow of the snake. In man, nerve cells are either scarce or absent in the ventricles. The cells are of four types: (1) The most common type is round or polygonal, sends out from three to ten dendrites, and gives off nonmedullated axis cylinders, some of which have been traced to muscle fibers. (2) A less common type, often found in nerve trunks, is round and has long dendrites and medullated axis cylinders, some of which may terminate in cardiac muscle (Woollard). (3) An uncommon variant of the first two types possesses dendrites which interlace with adjacent cells. (4) A rare type, rosette-shaped, has nonmedullated axis cylinders which appear to end in muscle fibers.

The cells of all types are found singly and in groups varying from a few cells, discernible only by aid of the microscope, to large ganglia readily seen with the naked eye. The ganglia are scattered diffusely under the pericardium of the atria and in the atrioventricular sulcus. The larger chains of ganglia are frequently found around the roots of the vessels. Large collections of nerve cells occur in the atrial wall of the posterior and anterior segments of the ventricular groove in man and other mammals. Anteriorly, these collections are most conspicuous between the root of the aorta and that of the pulmonary artery. In the lateral segments of the atrioventricular groove the nerve cells are few, and occur singly or in tiny groups. Nerve cells located within the nerve bundles are most numerous in the anterior part of the atrioventricular groove.

The nerve trunks, composed of medullated and nonmedullated fibers, extend from the atria to the ventricles in the region of the septum, both anteriorly and posteriorly (Woollard). In the atrioventricular groove and in the ventricles the nerve trunks from which the subendocardial and subpericardial plexuses of fibrils are found follow the coronary arteries. Woollard described fibrils which penetrate the muscle cells, and stated that the nerve fibrils which terminate in nonmuscular tissue have a sensory function.

Wilson[13] first gave an accurate description of the abundant nerve tissue which is present in the Purkinje bundle of the ungulates. All of the observers who have studied the regions of the sinoauricular and the atrioventricular nodes noted nerve cells in close proximity to the "nodes" and found nerve fibrils among their muscle elements. Recently, Nonidez[14] published an illustration showing numerous nerve fibrils lying among the muscle fibers in the His bundle of the dog. In our studies

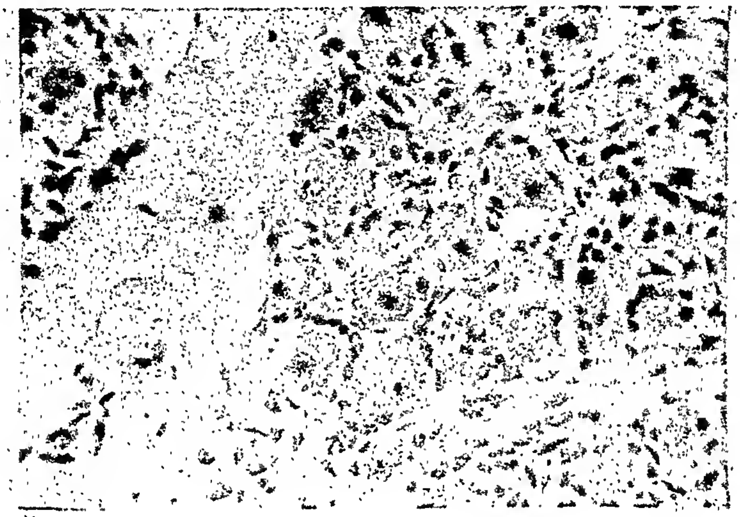
the region studied surprised us. Our observations are shown diagrammatically in Fig. 5; however, from our diagram one does not obtain a correct concept of the large number of nerve cells present. All sections contained nerve bundles and nerve fibers; more than two-thirds of them contained from one to fifty nerve cells. The cells were most numerous in the posterior and anterior septal segments of the atrioventricular groove, but were also found elsewhere in the sulcus. In the groove they occurred singly or in small groups, lying loose in the fatty tissue or inside of the nerve trunks. Ganglia appeared most numerous on the anterior and posterior surfaces of the atria (Fig. 6). Large collections extended from the very surface of the heart to the central fibrous body in the posterior part of the groove. Here they were more numerous on the atrial side, and appeared to have no immediate relation to nerve bundles. The only segment free from ganglion cells was the one which extended from the central fibrous body forward the length of the septal aortic ring. In front of this segment, between the aorta and the pulmonary artery, large collections of nerve cells were found in all hearts.

Fig. 7.—Nerve trunks in the atrioventricular groove.

Here they formed an almost continuous mass, extending between the two coronary arteries and lying on top of the anterior portion of the septum. It appears, as Woollard has reported, that the ganglion cells found in the groove on its lateral aspects are extensions of the masses found in the anterior and posterior part of the groove. The posterior mass of ganglia is a direct extension of the nerve tissue between the two atria and around the large veins. The abundance of nerve trunks found in this part of the heart is impressive (Fig. 7). Those found in cross section in the neighborhood of the coronary arteries are undoubtedly nerves following the vessels. In the nerve trunks, in the anterior part of the groove, nerve cells frequently occur (Fig. 6, *B*). Some of the trunks, which were cut longitudinally, probably extend into the ventricles. The nerves in the

In order to obtain more information about the relation of the intrinsic nerve tissue to the upper part of the ventricles, we made longitudinal microscopic sections of three human, and one canine heart in the region of the auriculoventricular sulcus. The blocks were cut to include both the atrial and the ventricular portions of the groove. The material was fixed in formalin, and sections were cut from both ends and the middle of each block. All sections were stained with iron hematoxylin because by this method the nerve cells and nerve trunks are readily

A.



B.

Fig. 6.—Nerve cells in the atrioventricular groove. *A*, Ganglion in loose fatty tissue. *B*, Ganglion in a nerve trunk.

recognized. No attempt was made to study the finer ramifications of the nerve fibers because such studies have already been made by several competent investigators whose observations are essentially in agreement. The heart of a dog was included in this study because we wished to compare the observations in man with those in the dog, and because immediate fixation of the dog heart after death eliminated possible errors due to post-mortem change. The richness of the nerve tissue in

as large and small collections and as individual cells into the atrioventricular groove. These nerve cells are most numerous in the posterior and anterior part of the groove. Most of the ganglia lie near the pericardium. Many collections of cells occur inside the atrioventricular nerve trunks in the anterior portion of the sulcus. Numerous nerve trunks follow the coronary arteries; other nerves extend from the atria to the ventricles posteriorly. Smaller branches sometimes follow the coronary arteries in the ventricles. Woollard and others have shown that the nerve trunks break up into pericardial and endocardial nerve plexuses, both in the atria and in the ventricles.

6. We, therefore, believe that the cardiac musculature is under a nervous control similar to that of other muscle tissue, and consider it physiologically unsound to draw conclusions concerning cardiac conduction without taking cognizance of the rich, intrinsic nerve system of the heart.

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ventricles are always found in the neighborhood of coronary vessels. We have found individual ganglion cells in the conus arteriosus, but nowhere else in the ventricles of carnivorous animals. Our study, however, has not been exhaustive.

In mammals an abundance of nerve tissue was found. This tissue consists of nerve cells, apparently limited to the pericardium of the atria and the atrioventricular sulcus; nerve trunks, passing from the atria to the ventricles; and pericardial and subendocardial plexuses of fine nerve fibrils in both the atria and the ventricles. The fibrils of these plexuses lie on the individual muscle fibers, and penetrate some of them (Woollard).

What is the function of these intrinsic nerves of the heart? Obviously, our study does not answer the question. Gaskell[15] held that the cardiac impulse has a nervous origin in the frog, and Carlson[16] showed that the intrinsic nerves of the heart originate and control cardiac contraction in the king crab. We have found ample morphologic support for the neurogenic theory in the hearts that we have examined.

CONCLUSIONS

1. The ridge fasciculus (the His bundle) is a slender muscle bundle in the upper part of the interventricular septum, measuring from 1 to 2 mm. in diameter. It originates in the ventricular portion of the central fibrous body (trigonum fibrosum), runs forward just underneath the mesial part of the aortic fibrous ring, continues caudally underneath the fibrous ring of the tricuspid valve in the fissure between the mesial and the anterior cusps, and extends downward toward the base of the septal papillary muscle. It does not bifurcate, and, therefore, has no left branch. It is not surrounded by a special connective tissue covering, but lies in intimate contact with other muscular elements of the septum from the place where it emerges from the canal in the central fibrous body to the base of the papillary muscle. In some hearts it is covered with muscle bundles which run obliquely across it. It is structurally identical with the other muscle fasciculi of the heart.

2. The ridge fasciculus has no special vascular supply. The ramus septi fibrosi (Haas), a branch of the coronary artery which supplies the ramus descendens posterior, enters the ventricular septum just behind the central fibrous body and probably supplies the arterial blood for the ridge fasciculus. It is possible that the ramus limbi dextri (Gross) may supply the lower part of the fasciculus.

3. We have not found any muscle connection between the fibers of the ridge fasciculus and those of the right atrium.

4. We have found no anatomic evidence to support the myogenic theory of cardiac conduction.

5. The heart has a well-developed, intrinsic nervous system consisting of nerve cells, nerve trunks, and networks of nerve fibrils. The nerve cells are found underneath the pericardium of the atria, and extend

in a general review of myocarditis, mentioned that in only three of the reports included in his review were tubercle (acid-fast) bacilli demonstrated.

Giant cells with radial inclusions have been reported only once in the myocardium. These inclusions of giant cells were described first by Goldman[7] in a dermoid cyst of the neck and, since then, have been observed in various viscera. From observations and experiments, Hirsch[2] concluded that the inclusions probably are a crystalline form of fat, such as palmitin or stearin, which had separated in the lesions from a liquid fat system containing cholesterol or substances with the physical properties of cholesterol, and that gradually, in the tissues, these crystals had become insoluble in the usual solvents for lipids.

CASE REPORT

A white woman, aged 65 years, entered St. Luke's Hospital Nov. 12, 1942, and died Dec. 3, 1942. In August, 1941, the patient had bundle branch block, but she was not decompensated. In August, 1942, in another hospital, a radical, right-sided mastectomy and axillary dissection had been performed. She had symptoms of coronary occlusion on the fifth hospital day. An electrocardiogram at that time revealed slight change from one made the previous year. She entered St. Luke's Hospital because of nausea and vomiting, sweating, salivation, and extreme weakness that began suddenly two hours before admission. The erythrocyte count was 4,620,000, the hemoglobin was 13.6 Gm., and the leucocyte count was 7,350. The urine contained more than 50 mg. per cent of albumin. An electrocardiogram showed partial A-V heart block and intraventricular block. The temperature was 98.4° F.; the pulse rate, 96; the respiratory rate, 28; and the blood pressure, 125/85. There were decreased breath sounds and dullness over the left side of the chest. The heart was grossly enlarged. The tones were irregular and of poor quality, with extrasystoles and gallop rhythm. Roentgenologic examination revealed compression of the lower lobe of the left lung, apparently caused by the enlargement of the heart. The transverse diameter of the heart was increased. Oxygen, aminophylline, digitalis, and sedatives were given as necessary. She was dyspneic, and her condition did not improve. On the tenth day in the hospital numbness in the right foot was noted, and examination showed that this extremity was colder than the left, was anesthetic to the ankle, and was cyanotic. This condition became worse. In the twentieth day in the hospital the left foot showed similar changes. The patient's temperature rose on the eighteenth day to 103.2° F., and the pulse rate increased to 100 per minute and to 160 terminally. She died on the twenty-first day in the hospital.

The essentials of the post-mortem examination (by Edwin F. Hirsch) of the trunk are as follows. The left lung was displaced by the markedly enlarged heart. The pericardial fluid was clear, yellow, and not increased in amount. The lining of the pericardium and epicardium was smooth. The heart weighed 385 grams. The diagonal measurement from the right auricle to the apex was 17.2 cm., and that across the base of the heart was 12.5 centimeters. The thickness of the myocardium of the right ventricle near the septum in front was 2 millimeters. The

Clinical Reports

EMBOLIC THROMBOSIS OF THE ABDOMINAL AORTA WITH TUBERCULOUS (HISTOLOGIC) LESIONS OF THE HEART CONTAINING GIANT CELLS WITH RADIAL INCLUSIONS

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AMONG the numerous published reports of tuberculous myocarditis and endocarditis there seems to be no record of a complicating mural thrombosis with embolism and thrombosis of the aorta and both common iliac arteries. This sequence of myocardial disease and complication is described in our report. The lesions in the myocardium have additional interest because some of the giant cells in the granulation tissues had radial inclusions. The association of giant cells with radial inclusions in granulomatous lesions of the myocardium resembles the conditions recorded by Diss[1] in the heart muscle of a woman, aged 64 years, with chronic tuberculosis of the lungs. The nodules he described in the myocardium consisted of epithelioid cells and giant cells, and several of the giant cells had asteroid inclusions. No acid-fast bacilli were found in the lesions. A review of the reports of giant cells with radial inclusions, additional descriptions, and an interpretation of the nature of the inclusions was published by Hirsch.[2]

Tuberculous myocarditis is not rare, and in some of the myocardial lesions acid-fast bacilli have been found. Townsend,[3] of Dublin (1832), is considered by some to be the first to describe tuberculous myocarditis. Horn and Saphir,[4] however, stated that Morgagni, in 1761, is generally regarded as the first to have recognized tuberculosis of the heart muscle. From 1832 to 1865 only a few reports were published. In 1865, Haberling, according to Anders,[5] collected twelve cases, some of which were of tuberculous pericarditis only. Sanger, Anders[5] stated, reported twenty-two cases, including three of his own. Anders' review,[5] in 1902, brought the total number reported at that time to seventy-two. Horn and Saphir[4] stated that Raviart had collected one hundred eighty-five cases of tuberculosis of the heart muscle in a review of the literature up to 1906. Of these one hundred eighty-five cases, Raviart considered one hundred twenty-one to be authentic. Saphir,[6]

From the Henry Baird Favill Laboratory of St. Luke's Hospital, Chicago, Illinois.
Aided by the Winfield Peck Memorial Fund.
Received for publication Nov. 17, 1943.

The anatomic diagnosis was: marked chronic fibroplastic myocarditis; mural thrombosis of the endocardium of the left and right ventricles of the heart; cloudy swelling of the myocardium; obturator thrombosis (embolism) of the aorta, the right and left common iliac arteries, the right and left external and internal iliac arteries, and the right and the left femoral arteries; recent infarcts of the kidneys, spleen, and left lung; obturator thrombosis of the smaller branches of the pulmonary arteries; fibrous and fatty changes of the coronary arteries, marked fibrous stenosis of the anterior descending branch of the left coronary artery; chronic fibrous tuberculosis of the lungs; calcification of the tracheobronchial lymph nodes and of the parabronchial lymph nodes; and gangrene of both legs and feet.

Sections of the lateral wall of the left ventricle which included portions of the mural thrombus were examined microscopically. Beneath the narrow epicardium was a wide zone of fat tissue, much of which was necrotic. Most of the myocardium was replaced by hyalinized fibrous scar tissue. Portions also had masses of granulation tissue composed of epithelioid cells, lymphocytes, and scattered multinucleated and vacuolated giant cells. Some of the later giant cells contained refractile radial inclusions (Fig. 1). The adjacent interstitial connective tissue also was infiltrated by granulation tissue. Along the endocardial margin there were granulation tissue thickenings containing lymphocytes, epithelioid cells, and a few Langhans giant cells (Fig. 2). On the endocardium here there were mural thrombi. The main portions of the thrombi were fibrin, with scattered erythrocytes, lymphocytes, and, in some places, polynuclear leucocytes. Sections of the granulation tissue in the myocardium were stained according to the Ziehl-Neelsen method for acid-fast bacilli. Two structures closely simulating acid-fast bacilli were found in these lesions. No acid-fast organisms were found in the endocardial lesions or in the thrombus material.

The dense tissue in the upper lobe of the right lung had a few scattered lymphocytes in a vascular fibroplastic tissue and several blood vessels. Toward the periphery there were diffuse aggregates of lymphocytes, epithelioid cells, and many multinucleated giant cells in a hyalinized fibrous stroma. Many of these giant cells also had large stellate refractile inclusions surrounded by small vacuoles containing refractile granules. A few large mononuclear cells contained particles of carbon. The parabronchial lymph nodes showed similar lesions, containing giant cells with stellate inclusions. The lesions in the kidneys, in the spleen, and in the lung were recent infarcts.

The histologic diagnosis was: chronic fibrous tuberculosis of the myocardium; chronic fibrous tuberculosis (histologic) of the lungs and hilar lymph nodes; recent infarcts of the kidneys, spleen, and lungs; etc.

Mural thrombosis with tuberculous myocarditis is not uncommon. According to Marshall,[1] cardiac thrombi were described first by Rokitansky, and were studied by Birch-Hirschfeld.[2] Birch-Hirschfeld[2] found, in the right ventricle of a man who had genitourinary and pulmonary tuberculosis, an adherent fleshy mass which at first was thought to be a primary sarcoma but microscopically was a tuberculous thrombus composed of [illegible] and organizing caseous thrombus material. Tarozzi[3] [illegible] over the papillary muscle of the tricuspid valve, about [illegible] had formed, in the body of a person who had tubercu-

pulmonic leaflets were smooth; the tricuspid leaflets had slight fibrous thickenings. The lining of the right auricle and the right auricular appendage was smooth. In the right ventricle, on the septal surface, there were fibrous plaques ranging to 1.1 cm. in diameter, and the lateral wall was rough and granular. The myocardium of the right ventricle, on surfaces made by cutting, was extensively replaced by fibrous tissue. The thickness of the lateral wall of the left ventricle along the septum behind was 0.9 cm. at the apex, and 1.5 cm. at the mitral ring level. There were slight fibrous thickenings of the mitral leaflets, especially of the anterior one. The lining of the left auricle and the left auricular appendage was smooth. Adherent to the lining of the lateral wall of the left ventricle behind the papillary muscles there were several partially organized mural thrombi; the largest was about 2.8 by 1.8 by 0.7 centimeter. Surfaces made by cutting the lateral wall of the left ventricle showed gray-red fibrillar tissue with marked cloudy swelling, and, on surfaces made by cutting the septal myocardium, nearly the entire wall was replaced by scar tissue that extended from 1.3 cm. above the apex to the base, and covered a region 6.3 by 6.8 centimeters.

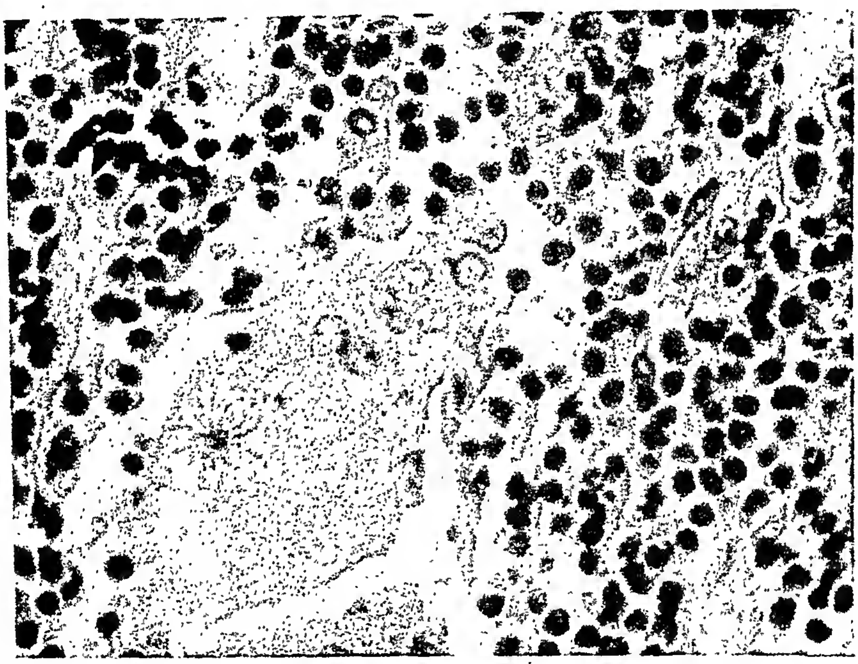

Fig. 1.—Photomicrograph illustrating a giant cell with a radial inclusion (×775).

Three small hyperemic gelatinous regions, about 1 cm. in diameter, were in the center of the scar. The anterior descending branch of the left coronary artery showed fibrous changes, and the lumen was markedly narrowed. There were moderate changes in other portions of the left and the right coronary arteries; the lumina were patent.

In the abdominal aorta, beginning at the upper margin of the celiac axis, there was a firm, ante-mortem, gray-red blood clot which completely filled the lumen and extended into the right and left common iliac arteries, the right and left external and internal iliac arteries, and the right and left femoral arteries. The first portion of the clot contained gray-white fibrinous material. There were recent infarcts in the kidneys, spleen, and the posterior inferior portion of the lower lobe of the left lung. In several of the smaller pulmonary arteries there were obturator thrombi (emboli).

Abstracts and Reviews

Selected Abstracts

Hyman, C: Filtration Across the Vascular Wall as a Function of Several Physical Factors. Am. J. Physiol. 142: 671, 1944.

A method for determining the filtration rate under controlled conditions is presented. This method depends on the continuous recording of the weight of a perfused preparation. The relationship between the osmotic pressure of the perfusion medium and the filtration rate is established for four colloidal systems: albumin, reconstituted plasma, pectin, and gelatin. The relationship between the perfusion pressure and the filtration rate is established for three types of perfusion medium: colloid-free saline, albumin solutions, and several dilutions of reconstituted plasma. The following conclusions may be drawn from the data presented:

a. There is an inverse linear relationship between the osmotic pressure of the perfusion pressure and the filtration rate when albumin or plasma is used.

b. There is a direct linear relationship between the perfusion pressure and the filtration rate.

c. The blood vessels of the preparation used can retain to a high degree molecules of the magnitude of albumin.

d. The blood vessels of the preparation used probably permit the passage of some fraction of the poly-dispersed gelatin system.

e. The effective osmotic pressure of a colloid in the vascular system is equal to the osmotic pressure determined in a physical osmometer only if the membrane used in the osmometer and the vascular wall both retain the same fraction of the colloidal system.

AUTHOR.

Evans, G.: Clinical Manifestations of Arteriosclerotic Disease. Practitioner 153: 129, 1944; Hoskin, T. J.: Diagnosis and Treatment of Coronary Diseases. Practitioner 153: 136, 1944; Wilkinson, K. D.: Diagnosis of Congenital Heart Disease. Practitioner 153: 146, 1944; Cookson, H.: The Treatment of Congestive Heart Failure. Practitioner 153: 155, 1944; Watkins, A. G.: Management of Rheumatic Heart Disease in Early Life. Practitioner 153: 161, 1944.

Each of the above articles discusses clinically the subject under consideration. The material is didactic but presents conservative opinion and the presentation is interesting. It should be important reading for those seeking information on each subject. The article on heart disease in early life is particularly important.

McCULLOCH.

Miller, H.: Spontaneous Mediastinal Emphysema With Pneumothorax Simulating Organic Heart Disease. Am. J. M. Sc. 209: 211, 1945.

Spontaneous mediastinal emphysema is briefly discussed with a short review of the pertinent clinical and experimental literature. Four new cases of spontaneous mediastinal emphysema associated with left-sided pneumothorax are described in which the clinical history, physical examination, or electrocardiographic examination simulated organic heart disease.

AUTHOR.

losis. Moser[11] stated that thrombi of the wall sometimes accompany large solitary tubercles, which by far are the commonest form of cardiac tuberculosis. Townsend[3] described a large tuberculous mass almost an inch thick in the wall of the left auricle. Death resulted from asphyxia because the mass compressed the pulmonary veins. Hoisholt, according to Moser, [11] in a case of pulmonary tuberculosis, found a lesion 3.5 cm. in thickness in the wall of the left ventricle of the heart. There was

A.

B.

Fig. 2.—*A*, Photomicrograph illustrating an endocardial mass of chronic granulation tissue (×198). *B*, Photomicrograph illustrating a perivascular mass of chronic granulation tissue in the myocardium (×198).

a similar mass in the upper part of the right auricle. Moser[11] observed a firm yellow thrombus at the apex of the left ventricle in a case of tuberculosis of the lungs. Pueschman, according to Anders,[5] described a caseous tubercle which extended through the wall of the right auricle

[illegible] cases were observed and described. In twelve of these cases the finding of a rumbling apical mid-diastolic murmur preceded by months or years the appearance of the classical presystolic crescendo murmur of mitral stenosis. In ten other cases of the 225, a similar mid-diastolic murmur was subsequently found to disappear. The appearance of accentuation of the apical first heart sound and of the pulmonic second sound in rheumatic patients should stimulate the clinician to search more diligently for definite signs of valvular disease, but of themselves are of little practical help in forecasting the development of mitral stenosis. The presence of apical systolic murmurs of slight intensity and of apical third heart sounds seem to have no [illegible] implications.

The results of the study suggest that in adolescent and young adult rheumatic patients a definite diagnosis of mitral stenosis should be made only on the finding of a long rumbling presystolic apical crescendo murmur ending in an accentuated first heart sound. The diagnosis may be suspected on the finding of definite apical mid-diastolic murmurs, but with the expectation that approximately half of these murmurs will disappear with further observation.

AUTHORS.

Loewe, L.: The Combined Use of Penicillin and Heparin in the Treatment of Subacute Bacterial Endocarditis. Canad. M. A. J. 52: 1, 1945.

Seventh Annual Louis Gross Memorial Lecture delivered at the Jewish General Hospital, Montreal.

Age and sex have no bearing on the outcome of therapy.

The type of organism, apart from the so-called streptococcus species is immaterial to the outcome of therapy, provided it is inhibitable by penicillin, within practical limits, 0.007 to 0.125 Oxford units).

If the patient is in good physical condition, the duration of the disease is less than three months, and the causative organism is sensitive to penicillin, a satisfactory result may be anticipated, barring accidents, in virtually every case.

AUTHOR.

Gay, P. F.: Rheumatic Fever of Childhood. Northwest Med. 43: 166, 1944.

Problems encountered in the diagnosis of one hundred seventy-eight cases of rheumatic fever admitted to the Children's Orthopedic Hospital of Seattle are [illegible].

The five manifestations of rheumatic fever are discussed, and the abstract of a case history including all five is given.

The onset of rheumatic fever and the frequency of a preceding episode in the one hundred seventy-eight cases are analyzed and reference is made to the part played by the *Streptococcus hemolyticus*.

The value of continuous institutional care during the toxic period is discussed. [illegible] in rheumatic fever patients, the age of onset, and other observations [illegible].

AUTHOR.

[illegible] J. E.: Asymptomatic Heart Disease in Young Adults. South. M. J. 37: [illegible] 44.

[illegible] of a group of [illegible] healthy candidates for military [illegible] organic heart disease was 0.5 per cent. The incidence of [illegible] generally accepted statistical data [illegible] only 16 per cent of the cases of [illegible] and only 8 per cent considered [illegible]

Evans, W.: The Unity of Paroxysmal Tachycardia and Auricular Flutter. Brit. Heart J. 6: 221, 1944.

A right pectoral electrocardiogram (CR_1) demonstrated the presence of A-V dissociation, usually 2:1, in twenty-seven consecutive cases of paroxysmal tachycardia. Further investigation is necessary before assigning this feature to all or to the majority of such patients.

In the meantime the finding suggests the common unity of paroxysmal tachycardia and auricular flutter, with auricular tachycardia as the essential mechanism of each, showing variations in rate and in the degree of A-V dissociation.

AUTHOR.

Szekely, P.: Chest Leads for the Demonstration of Auricular Activity. Brit. Heart J. 6: 238, 1944.

Special chest leads were used for the study of auricular activity and compared with the standard leads. The exploring electrode was placed in the third intercostal space at the right sternal border and paired with the right arm or left leg. The former lead was referred to as auricular Lead R; the latter, as auricular Lead F. Auricular Lead F was found to be more useful than auricular Lead R.

These special chest leads were studied in cases with paroxysmal tachycardia, with auricular fibrillation and flutter, and in a number with sinus rhythm. They often showed auricular waves to much better advantage than did the standard leads. It is suggested, therefore, that the recording of these leads is indicated in all cases in which there is doubt about the activity of the auricles.

No correlation was found between the size of the right auricle and the amplitude of the P waves as recorded in the auricular leads. It seems, therefore, that the amplitude of the P wave in the auricular leads is also determined by factors other than the size of the right auricle. The anatomic position of the right auricle in the thoracic cavity and its relation to the anterior chest wall are suggested as possible factors.

AUTHOR.

Tubbs, O. S.: The Effect of Ligation on Infection of the Patent Ductus Arteriosus. Brit. J. Surg. 32: 1, 1944.

The anatomy, physiology, and pathology of the ductus arteriosus are briefly reviewed.

Nine cases of subacute bacterial endarteritis complicating a patent ductus and treated by ligation are described; six of these patients are well today, from fifteen months to over four years after operation.

The technique of the operation is described.

The reason why ligation frequently results in cure of the infection is discussed.

The effect of ligation on infection of a patent ductus has been dramatic, although perhaps unexpected, and infection must now be considered an absolute and urgent indication for operation. Under these circumstances it is important that the supervention of infection should be diagnosed early; any patient with a patent ductus who runs an unexplained fever for more than two weeks should be suspected of this complication.

AUTHOR.

Boone, J. A., and Levine, S. A.: The Development and Interpretation of the Auscultatory Signs of Mitral Stenosis. J. South Carolina M. A. 40: 203, 1944.

During a study of 225 cases of "potential rheumatic heart disease" and "rheumatic mitral insufficiency" followed closely over a period of five to twenty-three years, the auscultatory findings leading up to a final diagnosis of mitral stenosis

With artificial respiration the systemic pressure falls during inflation, due to an increase of resistance of the pulmonary circuit. With artificial respiration and high hyperpressure the inflow to both ventricles is hampered in addition to the increased resistance of the pulmonary circuit, which determines the fall of the systemic pressure and the reduced pulse pressure in both circuits.

AUTHORS.

Proskauer, G. G., Neumann, C., and Graef, I.: The Measurement of the Blood Pressure in Rats With Special Reference to the Effect of Changes in Temperature. Am. J. Physiol. 143: 290, 1945.

The relation between blood pressure, cardiac rate, and the temperature of the rat has been investigated. Indirect (plethysmographic) and direct (Hamilton's optical manometer) methods for measuring the blood pressure were used.

The systolic pressure of trained, normal unanesthetized rats, as measured by a modification of the indirect method in which there is no change in the rectal or cutaneous temperature, was 65 to 95 mm. Hg at room temperature (24° to 28° C.). To avoid the elevation of body temperature that occurs when animals are held in containers with solid walls, an animal holder with walls of wire mesh was found useful.

Elevating the cutaneous and rectal temperatures of normal anesthetized or unanesthetized rats was regularly followed by a progressive rise in blood pressure. The more rapidly the cutaneous temperature was increased, the more rapid was the blood pressure response. Fluctuations in cutaneous temperature corresponded more closely in time and extent with the changes in blood pressure, than did the changes in rectal temperature.

Depressing the temperature of normal unanesthetized or anesthetized rats was followed by a fall of blood pressure; after thirty minutes or more the blood pressure rose again, occasionally to hypertensive levels. Cardiac rate rose and fell with the blood pressure except in heat stroke, when it remained accelerated after the pressor effect had disappeared.

AUTHORS.

Medoff, H. S., and Bongiovanni, A. M.: Age, Sex and Species Variations on Blood Pressure in Normal Rats. Am. J. Physiol. 143: 297, 1945.

Blood pressures in a series of one hundred and thirty Wistar Albino rats and thirty-three Wistar Gray Norways were determined. The Wistar Albinos exhibit a definite tendency toward higher blood pressures with increasing age. No sex differences in blood pressure were noted in the Wistar Albino rats. There are no significant blood pressure differences between these two species.

AUTHORS.

Dick, G. F.: Experimental Hypertension; Its Production in Dogs by Intravenous Injection of Streptococci. Arch. Path. 39: 81, 1945.

Hypertensive states comparable to essential hypertension and hypertensive renovascular disease in man have been produced in dogs by intravenous injections of streptococci and other bacteria.

AUTHOR.

Dexter, L., Haynes, F. W., and Bridges, W. C.: The Renal Humoral Pressor Mechanism in Man. I. Preparation and Assay of Human Renin, Human Hypertensinogen, and Hypertensin. J. Clin. Investigation 24: 62, 1945.

Methods for the preparation of hypertensin and of human renin and hypertensinogen free from hypertensinase have been described, together with their assay by modifications of the methods of Braun-Menéndez, Fasciolo, Leloir, Munoz, and Taquini.

AUTHORS.

By standardization of criteria as to what constitutes a significant abnormality and by more universal adoption of a more complete method of examination, much could be done to eliminate errors of diagnosis.

It is believed that individuals with organic heart disease, even in asymptomatic cases, should be acquainted with the presence and nature of their disease in order that they may properly adjust themselves to a routine of life designed to produce maximum efficiency for the longest period of time.

AUTHOR.

Moses, L. E.: **Mechanism of the Effect of Hyperthyroidism on Cardiac Glycogen.** Am. J. Physiol. 142: 686, 1944.

Methods were developed for accurate and consistent determination of heart rate, oxygen consumption, and cardiac glycogen in the white rat. A technique was also devised for the removal of large amounts of blood from the rat's tail. Standard "predictable" levels of heart rate and basal metabolic rate were established in 110 rats. After approximately two weeks of experimental manipulation, cardiac glycogen contents were determined and compared, in relation to the changes produced in heart rate and metabolic rate, with normal controls and with each other. Moderate hyperthyroidism was found to deplete heart glycogen to an extent directly related to the increase in heart rate but not closely related to the metabolic stimulation. Atropine and chilling (by depilation) decreased heart glycogen, in relation to the tachycardia produced, to a degree similar to that obtained in hyperthyroidism. Caffeine caused a smaller loss of heart glycogen, with reference to the stimulation of heart rate, than would have been predicted from the effects of thyroid, atropine, and chilling. This might have resulted from the increased blood pressure and the coronary dilatation characteristic of caffeine medication. Primary anemia produced a decrease in heart glycogen roughly correlated with the decline in hemoglobin content of the blood. Cobalt polycythemia seemed, to a slight extent, to protect the hyperthyroid heart from loss of its glycogen stores. The decrease in heart glycogen of nineteen hyperthyroid rats was participated in by both the left and right ventricles. Loss by the left ventricle was greater by an average of 37 per cent, but the variability of results, due to technical difficulties, renders this difference not statistically as significant as might be desired.

It is concluded that the decrease in heart glycogen by hyperthyroidism is not due to any specific "toxic" influence of the thyroid hormone. The suggestion is tentatively offered that the glycogenolytic action is exerted through a relative ischemia caused directly and indirectly by the increased cardiac activity.

AUTHOR.

Alberti, V. A., Segura, R. G., and Lanari, A.: **Mechanisms of Respiratory Variations of Arterial Pressure on the Pulmonary Circulation.** Medicina, Buenos Aires 4: 412, 1944.

The changes in pulmonary and systemic pressure induced by ordinary breathing and artificial breathing are studied without opening the thorax, without opening the thorax but with an exposed heart, and with thorax opened. The Hamilton's hypodermic manometer was used for pressure readings.

With ordinary breathing, pressure falls during inspiration in both the systemic and pulmonary circuits although somewhat delayed (two or three beats) in the former as compared with the latter.

The importance of the diminution of the intrathoracic pressure during inspiration is stressed, as a result of which there is an increase in the capacity of the pulmonary bed with a diminished flow to the left ventricle and a subsequent fall in the systemic pressure.

[illegible] the venous pump in man, are worthy of greater attention in investigations of the problem of shock; these studies must be made on the human being, preferably, rather than on other animals.

AUTHORS.

Jackson, R. L., Einstein, A. J., Blau, A., and Kelly, H. G.: Angle of Clearance of the Left Ventricle as an Index to Cardiac Size. Modified Technic for Its Determination and Range of Values for Normal Children. Am. J. Dis. Child. 68: [illegible], 1944.

[illegible] technique was established for determining the amount of rotation of the subject necessary to make the left lower border of the cardiac silhouette (left ventricle) clear the projection of the transverse processes of the spinal column (the first angle of clearance) and the left lower border of the cardiac silhouette clear the anterior border of the bodies of the vertebrae (the second angle of clearance) in fluoroscopic examination.

Judging from the data obtained by repeated examination to establish the reliability of the method, not more than 10 per cent of the single measurements vary more than 5 degrees from the true value for the subject. For eleven of the sixteen children for whom repeated measurements were made, the mean deviation from the true value was less than 3.5 degrees for both angles of clearance.

For 162 normal children examined to determine the normal values, the values for the first angle of clearance ranged from 38 to 67 degrees and for the second angle, from 46 to 86 degrees. The mean value for the first angle of clearance was 51.8 degrees and for the second angle of clearance, 63.2 degrees. The standard deviations were 5.8 and 7.4 degrees, respectively. Children with vertically placed hearts showed clearance at a smaller angle than children with transversely placed hearts. There are no significant differences in the angle of clearance of the left ventricle in relation to age or sex. Stocky children tend to have greater than average angles of clearance.

It is the belief of the authors that fluoroscopic examination to determine the angles of clearance of the left ventricle is valuable as a supplementary means of studying the heart if the examination can be repeated and the results of subsequent examinations can be compared. Any significant change from the original values could then be interpreted as a change in the size of the heart.

AUTHORS.

Gillesby, W. J.: Cardiac Tamponade. Report of Stab Wound in the Right Ventricle. Mil. Surgeon. 95: 2[illegible]4, 1944.

A case of stab wound of the right ventricle with penetration of the left pleural cavity is presented in detail. An extensive transpleural approach was used and is indicated as an "all-purpose" incision. Hyperventilation was used to prevent pulmonary complications. The pericardium was left open in communication with the left pleural cavity to permit effusion to drain into the pleural cavity. Electrocardiographic tracings taken postoperatively show only an inversion of the T wave in Lead IV.

AUTHOR.

[illegible], U. D., and Jaques, L. B.: Effect of Dicumarol Upon Plasma Fibrinogen. Am. J. Physiol. 14[illegible], 101, 1944.

[illegible] was determined in dogs injected with varying amounts of [illegible] administration of dicumarol has an effect on plasma fibrinogen as [illegible]. Large doses tend to lower the plasma fibrinogen [illegible]. These results are similar to those obtained [illegible]

AUTHORS.

Lendrum, B., Kondo, B., and Katz, L. N.: The Role of Thebesian Drainage in the Dynamics of Coronary Flow. Am. J. Physiol. 143: 243, 1945.

The coronary arteries were perfused in dogs' hearts obtained immediately after the animals were sacrificed, and the drainage into the coronary sinus, right auricle, right ventricle, left auricle, and left ventricle were measured. Special umbrella-like partitions were used to seal the A-V openings.

The averages and standard deviation of the percentage flows obtained were: coronary sinus, *36.4 per cent ± 11.8 per cent;* the right auricle, *24.5 per cent ± 6.5 per cent;* the right ventricle, *30.8 per cent ± 5.4 per cent;* the left auricle, *1.4 per cent ± 1.7 per cent;* the left ventricle, *7.0 per cent ± 3.3 per cent.*

Details of technique and errors of method were discussed.

The flow into the right ventricle via the Thebesian channels was shown to be of significant magnitude.

AUTHORS.

Opdyke, D. F.: The Survival of Dogs Treated With Neosynephrin During the Production of Hemorrhagic Shock. Am. J. Physiol. 142: 576, 1944.

Twelve dogs were subjected to hemorrhagic shock by controlled bleeding. Neosynephrin was infused during the severely hypotensive period (30 mm.) at a rate which maintained the level of blood pressure between 50 and 75 millimeters. At the end of the infusion period (thirty-four to forty-five minutes) the dogs were reinfused with their own blood, and the subsequent course of events observed. Eight of the dogs died in shock and one recovered from this treatment, while three dogs died of cardiac failure during the infusion of neosynephrin. The average survival time of the dogs dying in shock was 13.4 hours as compared with 5.3 hours in a control series.

It is concluded that any increase in peripheral damage due to an augmented vasoconstriction is compensated for by an increased flow of blood through the vital centers resulting in an increased survival time, but no permanent improvement. However, the use of pressor drugs during severe hypotension seems to be contraindicated because of the direct or indirect damage to the myocardium which may result from their use. The beneficial result of use of pressor drugs in the treatment of shock is questionable from a therapeutic standpoint.

AUTHOR.

Henstell, H. H., and Gunther, L.: Studies of Plasma Volume in the Human Being; Comparative Results of Reduction of Plasma Volume, Intramuscular Pressure and Venous Pressure in Surgical Shock. Am. J. M. Sc. 209: 187, 1945.

Peripheral circulatory failure in surgical shock may be evident with a normal and unchanged plasma volume. A decrease in plasma volume up to 590 c.c. is not necessarily followed by peripheral circulatory failure. Change in the clinical condition of the patient, for the worse or for the better, and the presence or absence of peripheral circulatory failure, coincide more closely with decline of, or the heightening of, intramuscular pressure, than with changes in the plasma volume. Peripheral circulatory failure may be manifest with a normal or with a decreased plasma volume, but not with an unchanged intramuscular pressure, which remains in the normal range. The circulatory failure is always associated with a lowered level of intramuscular pressure.

An inadequate peripheral circulation, despite a plasma volume decrease of at least 416 c.c., can be compensated and returned to adequacy with the restoration of a low intramuscular pressure to a higher level by the use of nikethamide. Changing increments of intramuscular pressure are an important factor in the dynamics of the peripheral circulation. The kinetics of the peripheral circulation as related to intramuscular pressure (the venopressor mechanism) and other forces that may consti-

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THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty eminent physicians who represent every portion of the country.

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The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

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The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

Thomas, W. C., and Harrison, T. R.: The Effect of Quinidine on the Mortality of Rats With Experimental Myocardial Injury. Am. J. M. Sc. 208: 756, 1944.

The results obtained from ninety-nine volunteer, hospitalized subjects indicate that the incidence of unfavorable reactions, with the possible exception of vomiting, is not increased by the concomitant administration of sulfathiazole and quinine or atabrine. The highest doses studied were: 6 Gm. of sulfathiazole daily for seven days; 2 Gm. of quinine bisulfate for the same period; and 0.3 Gm. of atabrine daily for five days.

The combination of drugs produced no detectable changes in the amount of hemoglobin or the total white blood count.

Quinine and atabrine produced only minor changes in the free and total sulfathiazole in the blood and in the urine.

AUTHORS.

Bliss, C. I., and Allmark, M. G.: Digitalis Cat Assay in Relation to Rate of Injection. J. Pharmacol. & Exper. Therap. 81: 378, 1944.

In the assay for digitalis the U. S. P. XII calls for adjusting the concentration of the injection fluid so that it will contain the estimated fatal dose per kilogram in 15 cubic centimeters. This is injected at the rate of 1 c.c. per kilogram every five minutes, and the average number of injections in an acceptable group of cats must not exceed limits of thirteen to nineteen for an official assay. To test the importance of this restriction, four groups, each of twelve cats, have been injected with dilutions containing 64, 80, 100, and 125 per cent, respectively, of the estimated fatal dose, in each case at the rate of 1 c.c. per kilogram. The experiment has been made with three different preparations of digitalis, requiring a total of one hundred forty-four cats.

In three experiments the lethal dose increased with the concentration of digitalis in the injection fluid which, in turn, controlled the rate of injection. The increase was statistically significant in two of the three cases. The relation between log-dose and log-concentration was linear and has been fitted by a straight line with an average slope of b = 0.20 = 0.05. In other words, a twofold increase in the concentration of tincture in the injection fluid increased the lethal dose in terms of the original tincture by approximately 15 per cent, apart from any other change in procedure. If the groups of cats comprising an assay were to require thirteen and nineteen injections, respectively, the greatest allowable difference, the percentage potency of the sample could be biased by 8 per cent through this factor alone. Since the relation between log-concentration and log-dose in these experiments is linear, the required concentration of the dilute solution could be decreased to the present minimum and yet not eliminate this factor. The potential bias could be reduced, however, by restricting the allowable difference in the average number of injections between the two groups of a single assay.

An alternative procedure for the cat assay has been examined with the present data, based upon the linear relation between log-concentration of the injection fluid and the log-minutes' survival time. In design and analysis it is equivalent to an assay based upon a graded response. The methods of statistical analysis suitable for self-contained assays have been extended, so that past experience can be used as it accumulates. When the present experiments were computed as test assays by this procedure, the estimated potencies agreed very well with the true value. The main advantage of the new technique is that it does not require as accurate a forecast of the potency of an unknown preparation as the official assay; its main disadvantage is that it would not reduce the number of cats needed to obtain a given precision. It should be of value, however, in the preliminary experiments which usually precede an official assay.

AUTHORS.

58.5 inches tall. There was no abnormal pigmentation of the skin or mucous membranes. The pupils were irregular, unequal, slightly dilated, and reacted sluggishly to light. The upper central incisors were typical Hutchinson's teeth. The tonsils were not obviously diseased. The thyroid gland was not enlarged. The thoracic contour and the lungs were normal. The apex beat was within normal limits. No thrills or abnormal pulsations were present. The heart rate (seated) was 180 per minute, and the beating was regular. The heart sounds were normal at the apex, but the pulmonic second sound was split. No murmurs were audible. The blood pressure was 80/60. No abdominal organs or masses were palpable. The knee jerks were hyperactive.

Laboratory Data.—There were no abnormalities in the blood cell count or in the urinalysis. The blood sugar level was 80 mg. per 100 c.c., and the blood urea was 14 mg. per 100 cubic centimeters. The blood Wassermann reaction was strongly positive (4 plus). Examination of the spinal fluid gave the following results: Wassermann reaction, anticomplementary; globulin, positive; cell count, 7; colloidal gold curve, 5555320000. On three occasions the basal metabolic rate was –25 per cent, –26 per cent, and – 13 per cent, respectively. The Mantoux tuberculin reaction was negative with 0.1 c.c. of 1:100 O.T. The vital capacity was normal (2,900 c.c.). A teleroentgenogram showed a hypoplastic type of heart. Roentgenograms of the knee joints showed nothing abnormal.

Additional Cardiovascular Studies.—Over a period of observation of six years the patient had a tachycardia which was invariably present when she was in the sitting and standing postures and frequently in the supine position. Of particular interest was the fact that the rate of the tachycardia varied with change in posture. For example, the pulse rate was usually about 120 per minute in the recumbent position, 150 in the sitting, and 180 in the standing. The range in pulse rate in the recumbent position was 80 to 140, in the sitting, from 108 to 180, and, in the standing, from 136 to 200 per minute. The difference between the recumbent and standing rates was never less than 40 beats per minute, and the rate in the sitting position was usually about the mean of the other two.

The heartbeat was always regular when she was in the erect posture. Rarely, dropped beats were noted when she was in the sitting position. The heartbeat was most often irregular during recumbency. Elevation of the foot of the bed accentuated the irregularity and retarded the pulse rate.

The change in pulse rate when the patient passed from the horizontal to the vertical position was instantaneous. When she changed from the vertical to the horizontal, however, the alteration in rate was sometimes abrupt and sometimes gradual. The pulse rate was accelerated by exercise only on the rare occasions when the rate in the erect posture was below 150 per minute. The application of oculobulbar or carotid sinus pressure did not retard the pulse rate or restore normal rhythm. There was no response to the Valsalva experiment.

It was possible, by administering digitalis or quinidine, to maintain the pulse rate at a normal level, i.e., about 90 per minute in the supine, and 96 in the standing, position, and to eliminate orthostatic symptoms. The blood pressure was usually between 90 and 100 mm. Hg, systolic, and 60 and 75, diastolic. Its postural variations, however, were within normal limits. The blood pressure was not significantly altered by digitalis or quinidine. The application of a tight abdominal binder did not influence the blood pressure or pulse rate.

Subsequent Course.—Due to the fact that the abnormalities of the spinal fluid persisted despite intensive antisyphilitic therapy, the patient was referred to the Greystone Park State Hospital for malarial therapy on June 21, 1943. The diagnosis was syphilitic meningoencephalitis, without psychosis. The patient was digitalized before and

American Heart Journal

VOL. 29 MAY, 1945 No. 5

Original Communications

CHRONIC AURICULAR TACHYCARDIA WITH UNUSUAL RESPONSE TO CHANGE IN POSTURE

REPORT OF TWO CASES

RALPH MILLER, M.D., AND JULIUS S. PERELMAN, M.D.
NEWARK, N. J.

FINE and Miller,[1] in 1940, presented a bizarre case in which, over a period of several years, so-called "paroxysmal" auricular tachycardia was invariably present as long as the patient sat or stood erect, and more often than not also persisted during recumbency. The rate of the tachycardia varied markedly on change of position. Shortly after this report was submitted, a second case, which was strikingly similar in most respects to the previous one, came to our attention at the Newark Health Department. The coincidence of observing concurrently these two cases of a chronic form of auricular tachycardia with unusual response to change of posture leads us to believe that this condition may not be unique, but that similar cases may have escaped recognition.

In the present communication we shall review both cases in detail, and attempt to delineate the symptom complex which distinguishes them.

CASE REPORTS

CASE 1.*—O. H., a 16-year-old white schoolgirl, was referred to the Cardiac Clinic in October, 1937, because of tachycardia. Since 1931 she had experienced recurrent attacks of pain and swelling of the joints of unknown cause. The knee, elbow, and wrist joints were involved symmetrically. In July, 1935, she was found to have prenatal syphilis, and appropriate therapy was instituted. The chief complaint was abnormal fatigability. There were but slight dyspnea and palpitation on unusual exertion or excitement. For several years she had noticed weakness, dizziness, and, occasionally, syncope upon standing erect. These symptoms were particularly annoying when she arose from bed after a sleep. She practically never perspired, and was greatly distressed by hot weather. The menses were scant and irregular, and were accompanied by moderately severe dysmenorrhea.

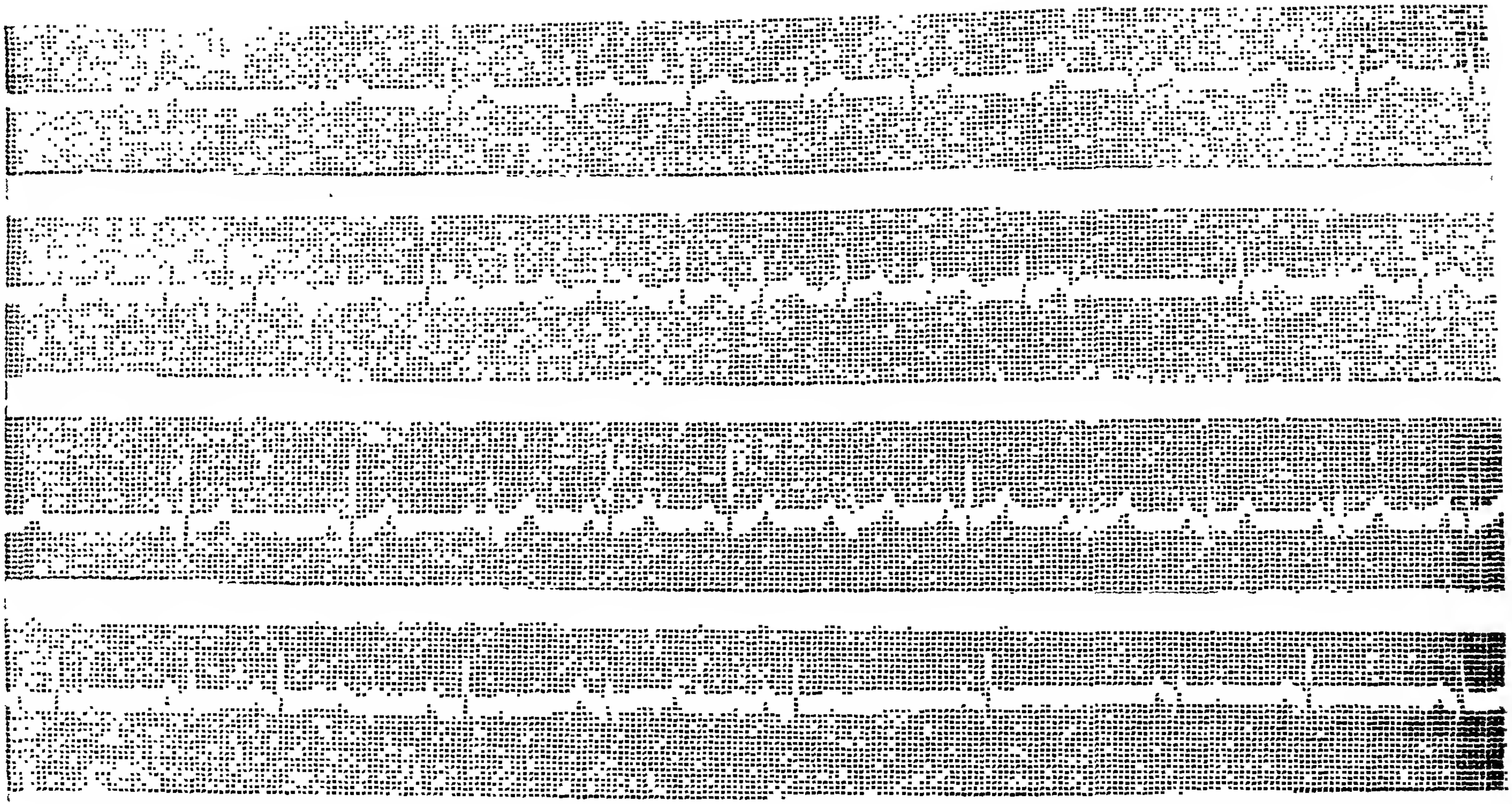
Her father was suffering from syphilis and pernicious anemia. Her mother and sister also had syphilis. A brother died of acute appendicitis.

Physical Examination.—The patient was a fairly well-developed adolescent girl of average intelligence. She weighed 104 pounds and was

From the Cardiac Clinic of the Newark Health Department, Newark, N. J.

Received for publication July 10, 1944.

*This case has been reported previously.[1] The history and physical signs are herein reprinted almost verbatim.



I A.

I B.

II.

III.

Fig. 3.—Supine position, immediately after Fig. 2. First two strips, Lead I, between which twenty cycles similar to last cycle of strip *A* and first cycle of strip *B* have been deleted. First two beats of sinus nodal origin. Following sequence of beats originated in lower center in sinus node. Second P wave of strip *B* is a transitional complex. Third beat of strip *B* inaugurates an ectopic rhythm with progressive increase in P-R interval. Eleventh beat of this run is blocked, and, following a pause, the ectopic center resumes command of the heart. Lead II, sinus bradycardia and shifting pacemaker. Lead III, short runs of auricular tachycardia.

during treatment. Malarial therapy was started on June 30 by inoculation with tertian malaria. She experienced eight chills. The pulse rate during the height of the fever varied from 78 to 146 per minute, and the pulse was of good quality. During her eighth chill the patient got out of bed suddenly, became weak and cyanotic, and fell unconscious. She died shortly afterwards, on July 19, 1943. Necropsy was not done.

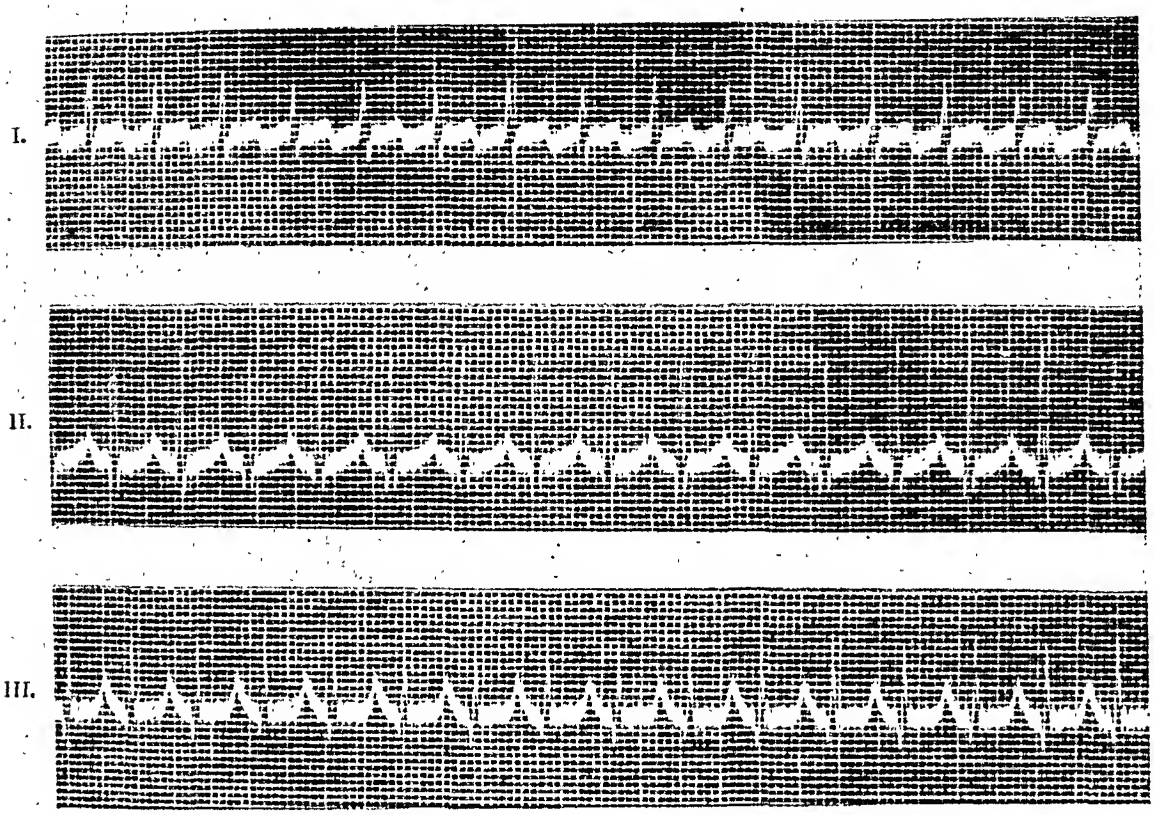


Fig. 1.—Case 1. Electrocardiograms taken Aug. 28, 1942, with patient in erect posture. Auricular tachycardia: rate 166 per minute. P_1 inverted, P_2 and P_3 upright. P-R interval about 0.16 second. Electrical alternation of R_1, S_1, Q_2, R_2, and Q_3.

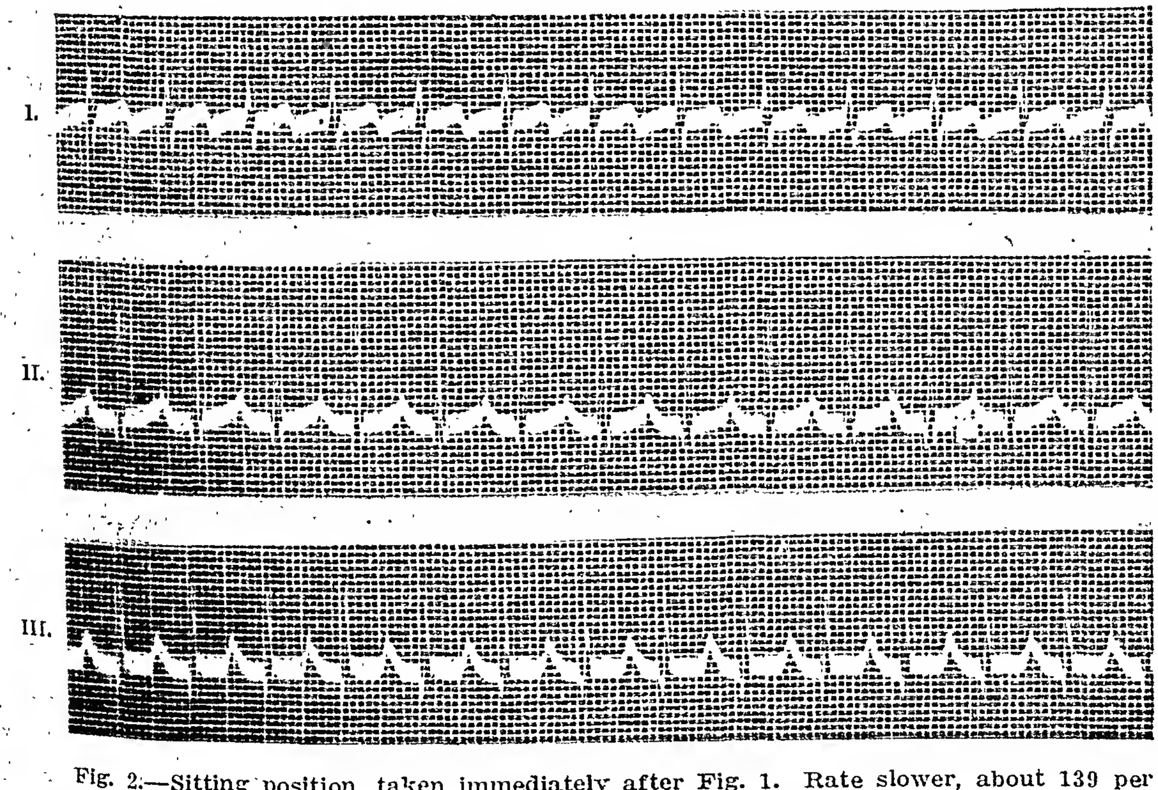


Fig. 2.—Sitting position, taken immediately after Fig. 1. Rate slower, about 139 per minute. P-R interval longer, about 0.20 second.

Analysis of Electrocardiograms.—Electrocardiograms which were taken on eleven occasions invariably showed orthostatic auricular tachycardia which changed rate on change of position. In the supine position there was either normal sinus rhythm, or, more frequently, auricular

casion did digitalis therapy temporarily abolish the tachycardia. There was no response to quinidine or potassium salts. A tight abdominal binder had no influence on the pulse rate. The pulse rate was not influenced by exercise, respiration, or oculobulbar pressure. The tachycardia persisted during sleep. There was no appreciable or consistent response to carotid sinus pressure. On one occasion carotid sinus pressure was followed by a break in the tachycardia and two normal sinus beats before the paroxysm was resumed. On another occasion 2:1 A-V block was produced. Both of these effects may have been fortuitous. The blood pressure was normal and showed the normal range of postural variations.

Subsequent Course.—The patient moved to Florida at the end of 1943, and, unfortunately, we have been unable to follow her any further. During the period of observation her general health remained excellent, and she showed no symptoms or signs except her persistent tachycardia.

I.

II.

III.

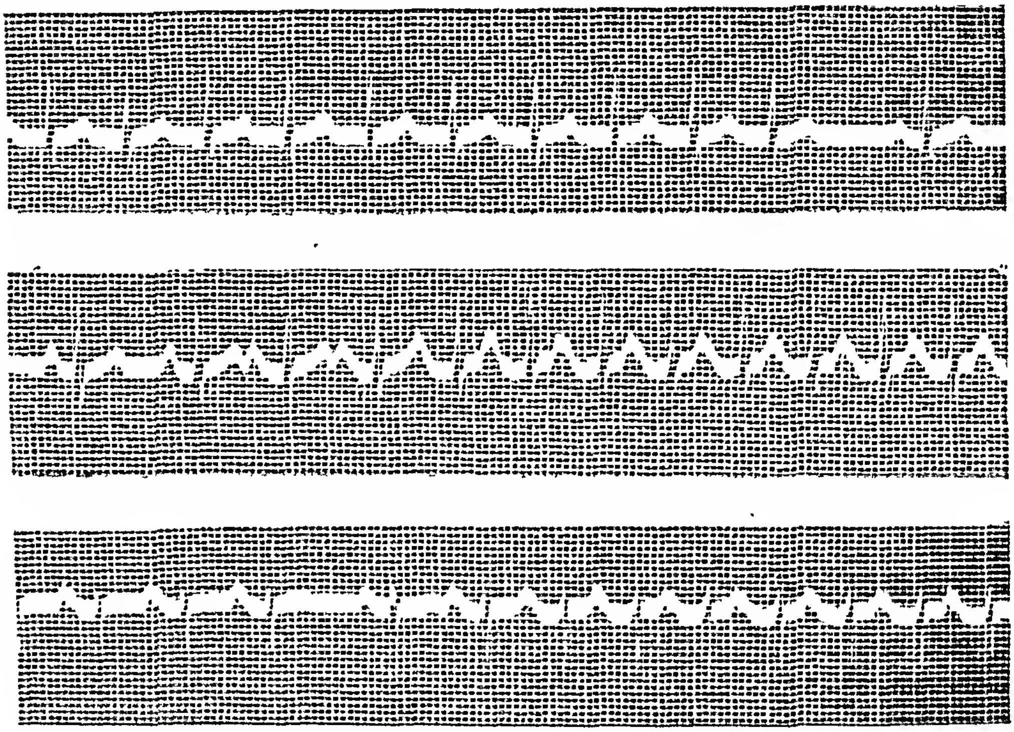


Fig. 7.—Immediately after Fig. 6, patient sitting. Rate of ectopic rhythm less, 158 per minute. One sinus nodal beat in Lead I, two in Lead II, and one in Lead III. P-R interval of normal sinus beats, 0.18 second. P-R interval of first ectopic beats, 0.22 second. Note gradual speeding up of rate of ectopic rhythm in Lead II.

Analysis of Electrocardiograms.—Electrocardiograms were obtained on thirteen occasions, in ten of which the influence of posture was investigated (Table I). There was invariably an auricular tachycardia which changed in rate with change of posture (Figs. 6, 7, and 8). The rate in the standing position ranged from 150 to 166 per minute; in the sitting position, from 125 to 158 per minute; and in the supine position, from 113 to 150 per minute. The maximum change in rate accompanying change from the vertical to the horizontal was 46 beats per minute, the minimum, 8 beats per minute. The change in rate was abrupt. Since in most instances the auricular complexes were superimposed upon the preceding ventricular deflections, the above rates are an approximation only. Accurate measurement of the auricular rate was also rendered impossible by the fact that the ventricular rate was inconstant because of varying A-V conduction. However, it was believed to be a fair assumption that, since the auricular rhythm was quite regular, the shortest R-R interval would closely approximate the true P-P interval, and the auricular rate was estimated accordingly.

tachycardia. During the tachycardia in the latter position when the rate was comparatively rapid, incomplete A-V block with the Wenckebach phenomenon was often noted. The electrocardiograms in Figs. 1, 2, and 3 are presented for more detailed analysis; they were taken Aug. 28, 1942, in the standing, sitting, and supine positions.

In the standing position (Fig. 1) paroxysmal tachycardia was present at a fairly constant rate of 166 per minute. The P wave was inverted in Lead I and upright in Leads II and III. The ectopic focus, therefore, was thought to be located in the left auricle.[2] Electrical alternation of the QRS complexes was noted in all leads. The P-R interval could not be measured accurately because the first portion of the auricular deflection was superimposed upon the preceding T wave. It was estimated at approximately 0.16 second.

In the sitting position (Fig. 2, taken immediately after Fig. 1) the auricular tachycardia persisted, but at a slower rate, i.e., about 139 per minute. The P waves differed very slightly in contour from those in the vertical position. This variation was ascribed to change in the electrical axis of the auricles with change in position, rather than to a shift of the ectopic focus. The P-R interval was longer than that in the preceding position. It was estimated at about 0.20 second.

II.

II.

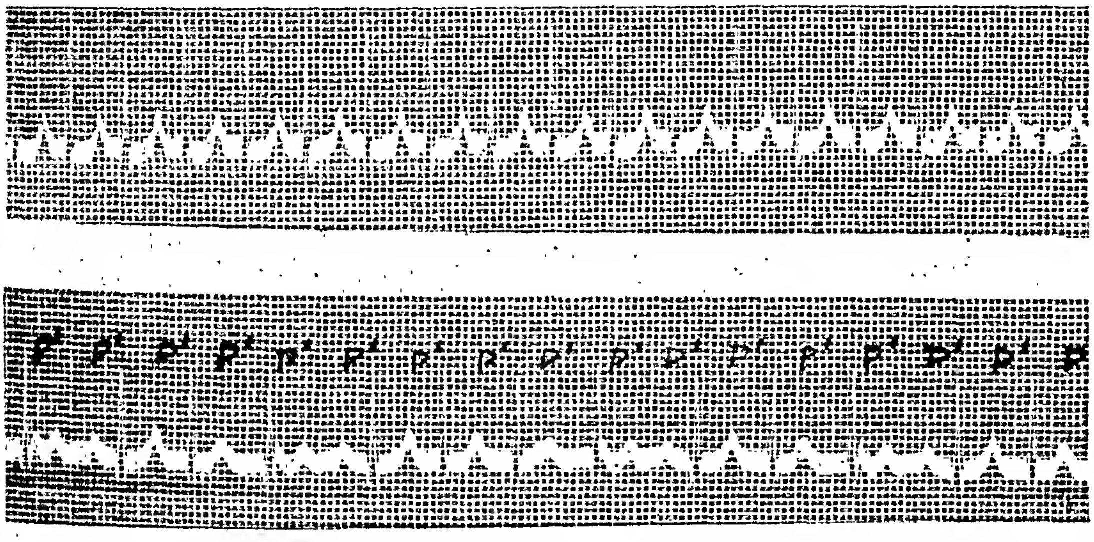
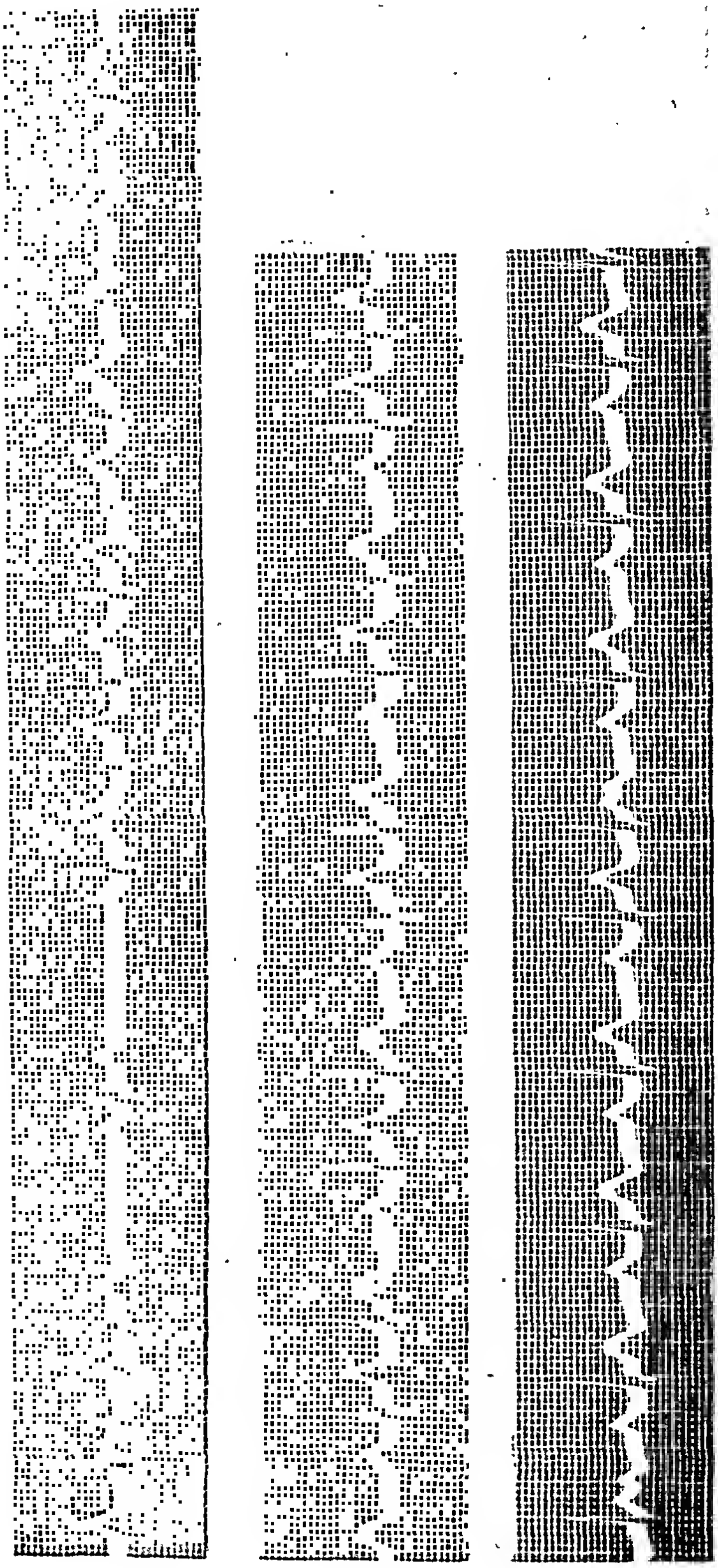


Fig. 4.—Oct. 13, 1939. Lead II. Upper tracing, patient standing. Auricular tachycardia, rate 176 per minute. Lower tracing, immediately afterwards, patient lying down. Auricular rate 170 per minute, incomplete A-V block with Wenckebach periods.

The electrocardiograms in the supine position (Fig. 3, recorded immediately after the preceding figure) were of special interest. In Lead I the first two beats were in response to the normal sinus pacemaker. The P wave was upright and of normal configuration, and the P-R interval was 0.16 second. The R-R cycle was 1.21 seconds in duration, corresponding to a heart rate of 50 per minute. After the second beat there was a shift to a secondary pacemaker lower down in the sinus node. The P wave which originated in this focus was lower in voltage, shorter in duration, and more sharply peaked than the normal. There was no change in the P-R interval. The rate was faster, about 74 per minute, and there was slight sinus arrhythmia. The wandering of the pacemaker in this instance must be ascribed to an enhanced irritability of the lower nomotopic center, rather than to a vagal effect, which is characterized by a decrease in the heart rate as the pacemaker descends toward the A-V node. There ensued a series of thirty-one beats from this focus, twenty of which have been deleted between strips *A* and *B* of Lead I. The second auricular complex in strip *B* was probably a transitional beat. The third auricular complex was inverted, and therefore ectopic in origin. It inaugurated a short run of paroxysmal tachycardia, at a rate of 107 per minute. The last auricular impulse of this

were of lower voltage than the normal P waves, whereas, in Leads II and III, they were taller and broader. They were followed by a well-marked auricular T wave, which caused a distinct sagging of the auricular S-T segment. The P-R interval corresponding to these abnormal



II A.

II B.

II C.

Fig. 9.—Sept. 23, 1942. Lead II, supine position. *A*, Note termination and onset of auricular tachycardia. P-R interval of first beat of tachycardia about 0.24 second. Well-marked auricular T wave after ectopic auricular beats. Progressive increase in P-R interval with, finally, two successive beats dropping out. P-R interval of next conducted beat about 0.26 second. *B*, Auricular tachycardia, 3:2 A-V block. *C*, Auricular tachycardia, 2:1 A-V block.

complexes was prolonged, and exceeded 0.20 second. This delay in the P-R interval was interpreted as indicating that an abnormal pathway had been taken by the wave of excitation in passing from the ectopic focus to the A-V node, rather than prolonged A-V conduction, because, even

The series of electrocardiograms shown in Figs. 6, 7, and 8 were especially selected from long strips to demonstrate the termination and onset of the tachycardia in the standing, sitting, and supine positions. In the illustrations several normal sinus beats are seen. The P-R interval corresponding to them was within normal limits, but varied with change of posture. There were very few normal auricular complexes throughout all of the electrocardiograms which were taken. In fact, only eighteen individual complexes of this nature were discovered out of a total of 2,312 auricular beats. On no occasion were more than two normal beats present in sequence. Two normal beats were found in the standing position, nine in the sitting, and seven in the supine. The runs of abnormal auricular beats ended in a postparoxysmal pause, and the first ectopic beat was premature. The aberrant P waves which gave rise to the tachycardia showed the following characteristics. In Lead I they

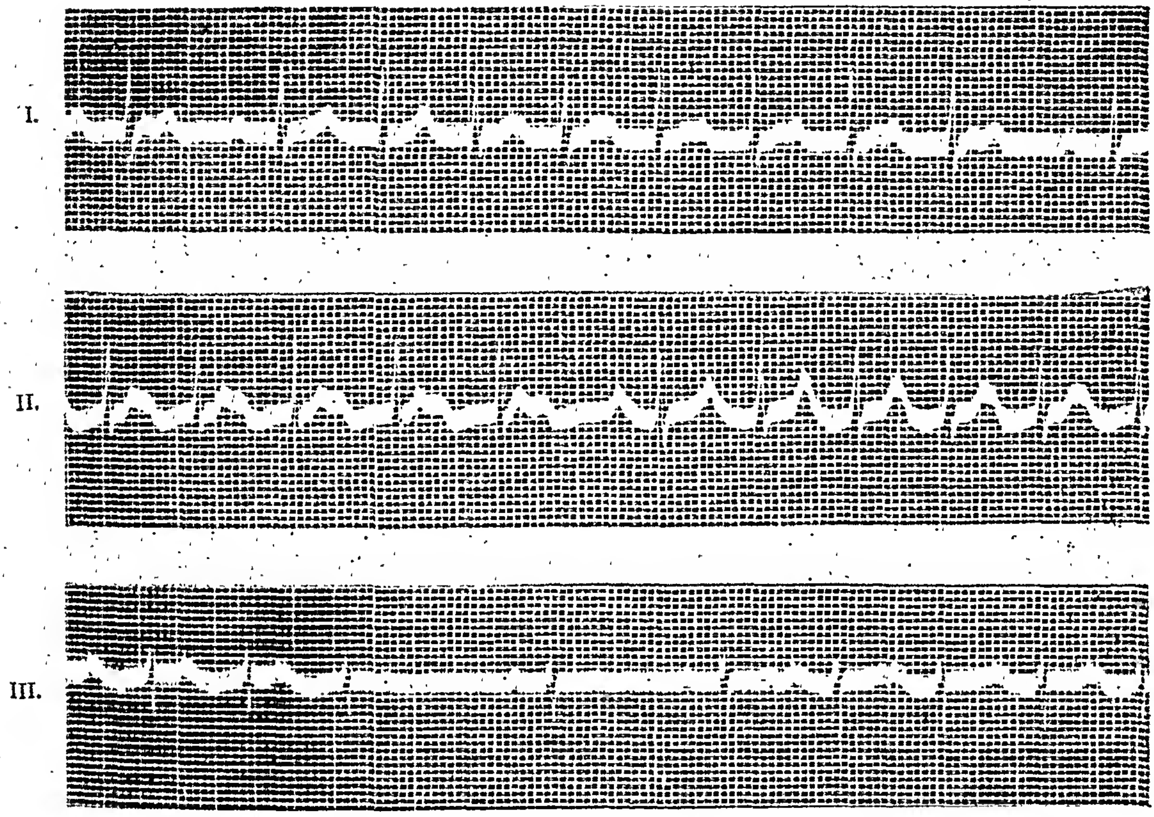


Fig. 8.—Immediately after Fig. 7. Patient supine. Further decrease in rate of auricular tachycardia, 130 per minute. Two normal sinus beats in Lead III, with P-R interval of 0.20 second. P-R interval of first ectopic beat, 0.24 second. (Note P-R interval of both normal and ectopic beats longer in recumbency than in sitting or standing positions.) Incomplete A-V block, with Wenckebach phenomenon during tachycardia.

TABLE I

ANALYSIS OF ELECTROCARDIOGRAMS IN CASE 2 WITH RESPECT TO RATE, PRESENCE OF DROPPED BEATS, AND NUMBER OF NORMAL SINUS BEATS IN THE STANDARD POSITIONS

DATE	AURICULAR RATE			DROPPED BEATS			NORMAL SINUS BEATS		
	STANDING	SITTING	SUPINE	STANDING	SITTING	SUPINE	STANDING	SITTING	SUPINE
11/15/40	158	150	125	-	-	-	1	0	0
12/14/40	166	158	133	-	-	+	0	1	0
2/13/41		125			+			1	
3/26/41	150	125	113	+	+	+	0	0	0
8/27/41	150	136	117	-	-	-	0	0	0
5/ 7/42	154	150	122	-	-	-	0	0	0
6/18/42		120			+			3	
7/ 8/42	158	150	117	-	-	-	0	0	0
7/23/42		150			-			0	
8/ 3/42	166	150	120	-	-	-	0	0	0
9/16/42	166	158	130	-	-	+	1	4	2
9/23/42	158	150	150	-	-	+	0	0	5
9/30/42	160	136	130	-	+	+	0	0	0

cases satisfied the following criteria for the diagnosis of paroxysmal auricular tachycardia: (1) The onset and termination of the tachycardia were abrupt. (2) It ended with a postparoxysmal pause. (3) The first auricular beat was premature. (4) The P waves were anomalous. (5) The rhythm in a given posture was fairly constant. (6) With certain exceptions, the arrhythmia did not exhibit the sinus reactions.

The possibility of a nomotopic rhythm may be excluded by the form of the auricular complexes. In Case 1 the P wave was inverted in Lead I and upright in Leads II and III, which suggested a locus in the left auricle.[2] In Case 2 the ectopic waves were higher than normal in Leads II and III, and consequently probably arose in the cranial portion of the right auricle. The absence of a consistent response to the sinus reactions in both cases and the response to digitalis and quinidine therapy in Case 1 also point to an ectopic origin of the tachycardia.

The tachycardia differed from typical paroxysmal auricular tachycardia in two important respects. First, since it occurred invariably as an orthostatic phenomenon and most of the time in the recumbent position as well, it was, in effect, the dominant and usual rhythm of these two hearts, or, in other words, it was a chronic arrhythmia. In this connection we may make mention of the fact that paroxysmal auricular tachycardia in many ways seems to be related closely to auricular flutter and fibrillation, and is possibly due to the same mechanism. Both of the latter may occur in either a paroxysmal or chronic form. Second, it did show some response to the sinus reactions. The rate of the tachycardia varied markedly with change in posture. Rarely, in Case 1, it showed some response to exercise. Carotid sinus stimulation, however, was without effect upon the auricular arrhythmia.

Little of fundamental importance has been added to our knowledge of the mechanism of paroxysmal auricular tachycardia since Lewis[6] reviewed the subject in 1925. Two main theories have been advanced in explanation of this arrhythmia, namely, (1) the theory of re-entry, of which circus movement is a variant, and (2) the theory of parasystole.

The theory of re-entry must be considered untenable unless the main objection, the presence of an isoelectric interval, be disposed of, as emphasized by Lewis.[6] Ashman and Hull,[7] and, more recently, Barker, et al.,[4, 8] attempted to dispose of this objection by suggesting either that the circus movement might involve in part of its pathway one of the auricular nodes, or that some part of the pathway might be so small that its action potential would not register in the electrocardiogram. We have been unable to reconcile the observations in our cases with this concept for the following reasons: (1) In our Case 1, as well as in several other reported cases of auricular tachycardia, the P wave was inverted in Lead I and upright in Leads II and III, presumably indicating that the impulse originated in the left auricle. If the circus pathway involved one of the nodes, the inscription of the auricular complex would begin at the moment the impulse made its exit from the node, and it is not conceivable that the foregoing P-wave pattern could result. As a possible rebuttal to this point, Ashman and Hull[7] called attention to an interesting observation by Glomset and Glomset,[9] namely, that tissue arrangement similar to that found in the region of the sinoauricular

when two ventricular beats dropped out (Fig. 9, *A*), the P-R interval of the first succeeding conducted beat was still lengthened. If the P-R delay were due to relative refractivity of the junctional tissues, recovery should have been expected after the rest period during the dropped beats. These abnormal auricular complexes were believed to be of ectopic origin for the following reasons: (1) distinctly aberrant appearance, (2) higher voltage than the normal sinus beats in Leads II and III, and (3) increased P-R interval. If these beats were of sinus nodal origin, with the pacemaker shifting to the lower portions of the node, the P waves should have been lower in voltage in Leads II and III, and the P-R interval, if altered, should have been shorter. It may be concluded, then, that the tachycardia was heterotopic in origin, and that its center was situated in the cranial portion of the right auricle. The ventricular complexes during the tachycardia were identical with those of the normal beats. Occasionally short periods of alternation of the QRS complexes were noted (Fig. 6).

Frequently, dropped beats, with or without Wenckebach periods, were present. At times only occasional beats dropped out, but at other times there was 3:2 or 2:1 block (Fig. 9, *B* and *C*). Incomplete A-V block was encountered only once in the standing position, four times in the sitting, and five times in the supine position. This phenomenon, in contrast to the prolongation of the P-R interval, is a definite indication of disturbed A-V conduction, functional in nature. It is probably the result of a combination of two factors, namely, fatigue, due to rapidity of the rate, and increased vagal tone, which accounts for its greater frequency during recumbency. On several occasions electrocardiograms were taken with the head of the table depressed at an angle of 30 degrees. This caused the auricular rate to be retarded below that in the supine position and increased the tendency to dropped beats.

Comment on Case 2.—This case was strikingly similar in most respects to the first one. In fact, the presence of a tachycardia which changed in rate upon change of position, without responding to the other sinus reactions, and with dropped beats in the supine position, led us to suspect its true nature clinically before securing electrocardiographic confirmation. Apparently this patient experienced no disability as a result of her tachycardia.

DISCUSSION

The arrhythmia which was present in these two cases was characterized by the following features: (1) chronicity. The tachycardia was invariably present when the patient was in the standing or sitting positions, and most often in the supine position, as well. (2) The arrhythmia originated in an ectopic auricular focus, in one instance in the left auricle, and, in the other, in the cranial portion of the right auricle. The tachycardia varied remarkably with change in posture. (4) The arrhythmia could not be terminated by carotid sinus stimulation. (5) Digitalis and quinidine therapy restored normal rhythm in Case 1. In Case 2 digitalis restored normal rhythm on only one occasion and quinidine was without effect. (6) Incomplete A-V block occurred in both cases, most commonly in the supine position. (7) Electrical alternation was observed in both cases.

These two cases are so bizarre that doubt must arise as to whether they actually fall into the category of paroxysmal auricular tachycardia. Case 1 has been cited twice since its publication, by Barker, et al.,[4] and Decherd, et al.[5] Both of these groups accepted it as an example of paroxysmal auricular tachycardia with incomplete A-V block. These

gressively as the patient changed position from the standing to the sitting, and from the sitting to the supine.

Electrical alternation was noted in both cases when the rate was excessively rapid.

The fact that we have had the experience of observing concurrently two bizarre cases of such striking similarity may have been a mere coincidence. However, it is quite possible that other cases of this nature may be overlooked and clinically may be mistaken for simple sinus tachycardia. If the electrocardiogram is recorded in one position only, and, as is *common practice, in the recumbent position, normal* sinus rhythm might be present, or, if the tachycardia should be in progress, the ectopic P waves may appear to be normal unless they happen to be markedly aberrant. If it were routine to take electrocardiograms in the three positions, standing, sitting and supine, in all atypical tachycardias, we believe more cases of this nature would be brought to light.

SUMMARY AND CONCLUSIONS

1. Two unusual cases of auricular tachycardia are presented. They fulfilled the electrocardiographic criteria for the diagnosis of paroxysmal auricular tachycardia, but differed from the classical type in two important respects, namely, the arrhythmia was chronic and it varied with change in posture.

2. The tachycardia was invariably present in the standing and sitting positions, and was present more frequently than normal sinus rhythm in the recumbent posture.

3. The rate of the tachycardia varied markedly on change of position. It was most rapid in the vertical, and slowest in the recumbent, position. One patient showed an occasional response to exercise, and also, in this case, the tachycardia could be abolished by digitalis or quinidine therapy.

4. In neither case was there any consistent response to carotid sinus stimulation.

5. In both cases there were clinostatic incomplete A-V block and orthostatic electrical alternation.

6. This symptom complex should be suspected clinically whenever there is a persistent orthostatic tachycardia which changes rate markedly on change of position, which does not respond to the other sinus reactions, and which is characterized by sudden breaks in rhythm. Electrocardiographic studies in the various postures should be carried out in these cases.

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node occurs in the left auricle around the mouths of the pulmonary veins, and suggested that possibly a circus movement could be set up in this region. (2) The rate of the tachycardia in the supine position was comparatively slow. On one occasion it was approximately 100 per minute (Fig. 5), with a corresponding P-P interval of 0.60 second. Since the auricular complex was 0.08 second in duration, the auricular isoelectric interval measured 0.52 second. It is hardly possible that the impulse would be delayed to such an extent in traversing the nodal tissues. (3) The change in rate on change of posture was too extreme to be explained reasonably on the ground of alteration of conductivity through the nodes or circus pathway. (4) An interesting phenomenon has been pointed out in Fig. 3. There was a break in the auricular tachycardia, and, after the postparoxysmal pause, the ectopic pacemaker resumed command of the heart. The first beat of the latter sequence could not be due to re-entry of the previous beat, but must be accepted as an impulse of spontaneous origin. This is an irrefutable argument against the possibility of re-entry in this particular case.

We believe that the theory of parasystole may be more applicable to our cases. The only convincing evidence for parasystole obtains in those rare instances in which the interval between ectopic beats is an exact, or nearly exact, multiple of a least common denominator, and when the ectopic beats appear at intervals which bear no fixed relationship to the normal sinus rhythm. These rigid criteria were not met in our cases. If, however, it be assumed that the rate of a parasystolic center might vary markedly in response to extracardiac influences, practically all cases of premature beats or paroxysmal tachycardia could be explained, although the proof of existence of parasystole would, in the process of accepting such an assumption, become all the more elusive.

The explanation of the arrhythmia in our cases, then, may be somewhat as follows: A parasystolic auricular focus was in continuous activity. There was a low degree of exit block, and, therefore, the parasystolic rhythm was the dominant one most of the time, and invariably in the upright position. It must be further assumed that the ectopic focus was under partial control of the extrinsic cardiac nerves, and responded in some degree to variations in vagal tone. The onset of the tachycardia in the upright position was thought to be due to a diminution in the tone of the vagus. Slowing of the rate in the sitting position was assumed to be due to reflexes from the lower extremities. Further retardation of the pulse or termination of the tachycardia in the recumbent or head-down position would coincide with additional vagal stimulation, either directly or reflexly through the carotid sinus by the sudden rush of blood to the head.[10]

The occurrence of incomplete A-V block in the two cases is of particular interest. In the first case it was found almost exclusively in the horizontal position, and, in the second, most frequently in this position. Clinostatic A-V block has been reported rarely, and has been explained as a postural vagal effect.[11, 12] Block occurred in the first case in the recumbent position only when the rate was relatively rapid. Therefore, the block resulted from a combination of two factors: fatigue due to rapid rate, and enhanced vagal tonicity. In Case 2 the P-R interval of both the normal sinus beats and the ectopic beats increased pro-

that he had had "left bundle branch block" in his electrocardiogram on several examinations since 1940. The current tracings appeared identical to previous electrocardiograms.

On examination, his blood pressure was 138/84. The peripheral arteries were normal. The fundi showed no evidence of retinal vascular disease. The heart size was normal. The heart rhythm was regular, and no murmurs were heard. An exercise tolerance test was normal. The sedimentation rate was 5 mm. (Westergren method). The blood and urine were normal. The blood nonprotein nitrogen was 31 mg., and the sugar, 99 mg., per cent. The blood Kahn reaction was negative. The heart size was normal on roentgenologic examination. An electrocardiogram (Fig. 1) showed the short P-R interval, of 0.10 to 0.12 second, and long QRS interval, of 0.16 second, which are characteristic of this condition. Atropine and exercise had no significant effect upon this electrocardiogram. Because the patient was a young physician, with infrequent attacks of paroxysmal tachycardia which were promptly controlled by carotid sinus stimulation, he was accepted for limited duty in the Army, confined to the continental United States.

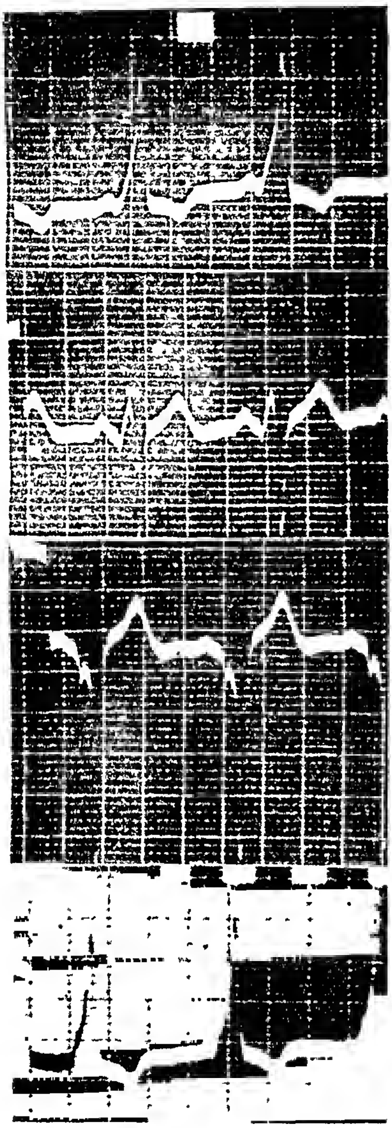

Fig. 1.—Case 1. Description in text.

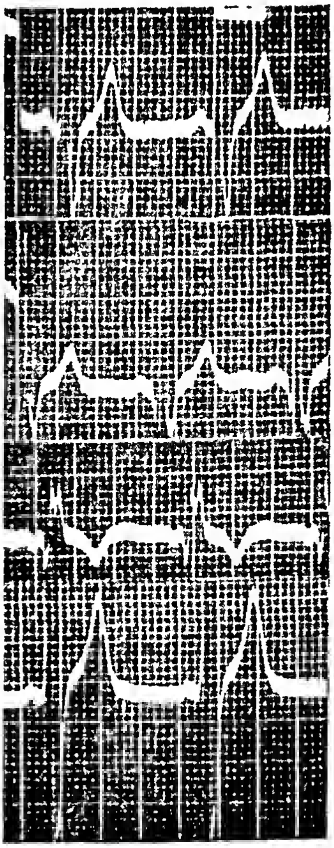

Fig. 2.—Case 2. Description in text.

Case 2.—This patient was a 30-year-old white man, also a physician. There was a strongly positive history of vascular disease in his family. His father has angina pectoris and his mother has hypertension. The only significant previous illness was cystitis, in 1931, after a lower urinary tract operation for hypospadias. He had had slight elevation of his blood pressure on several examinations during the preceding seven years. The highest reading, to his knowledge, was 170/110. He stated that he had an electrocardiogram at the age of 23 years which showed "delayed interventricular conduction time." That tracing was not available to us, but he stated that it appeared similar to the present electrocardiogram.

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WOLFF-PARKINSON-WHITE SYNDROME

Report of Five Cases

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THE electrocardiographic syndrome of a short P-R interval with a long QRS complex in patients who are subject to attacks of paroxysmal tachycardia was first described by Wilson,[1] in 1915. Isolated cases were then reported by Wedd[2] and Hamburger.[3] It was not until 1930 that Wolff, Parkinson, and White[4] focused attention upon this clinical entity by reporting a series of eleven cases. They emphasized the benign nature of the condition. Since then, there have been several case reports from different parts of the world. The largest group of cases (twenty-two) was reported by Hunter, Papp, and Parkinson,[5] in 1940. They stated that this syndrome constituted 5 per cent of their cases of bundle branch block, and was present in 5 per cent of their patients who were subject to paroxysmal tachycardia. They collected one hundred nine cases from the literature.

Recently, five cases have come to our attention, two with unusual features. Three of the cases were observed in the Army. The benign nature of the condition had not been recognized on previous examinations. The important factor in ascertaining whether these patients should be retained in the Army or returned to civilian life depends upon the frequency and disability produced by the attacks of tachycardia, and not on the bizarre appearance of the electrocardiogram. If the attacks of tachycardia are infrequent and of short duration, and stopped promptly by vagus stimulation or abolished by quinidine, these patients may perform useful service in the Army. The purpose of this paper is to report the cases that we have observed.

CASE REPORTS

Case 1.—This patient was a 29-year-old white man. There was a strongly positive history of vascular disease in his family. His father, mother, and brother have hypertension. There was no past history of rheumatic fever, chorea, syphilis, or hypertension. He had had "spinal meningitis" at the age of 15 years, with an uneventful recovery. His chief complaint was of eight attacks of palpitation since February, 1940. Each attack lasted only a few minutes, and the onset of each was sudden. The attacks stopped promptly when he held his breath or applied stimulation to the carotid sinus. The patient, a physician, stated

Received for publication July 17, 1944.

shows normal sinus rhythm, with extrasystoles characteristic of the Wolff-Parkinson-White type, occuring as bigeminy in Lead II. Fig. 5 shows a strip of Lead II. There are normal beats, ventricular extrasystoles, and extrasystoles similar to the Wolff-Parkinson-White beats leading to paroxysmal auricular tachycardia.

This patient's attacks of tachycardia were controlled by quinidine. He was not thought to be incapacitated by the infrequent attacks of tachycardia, which were controlled by quinidine. He was therefore reclassified to a limited duty status, confined to the continental United States.

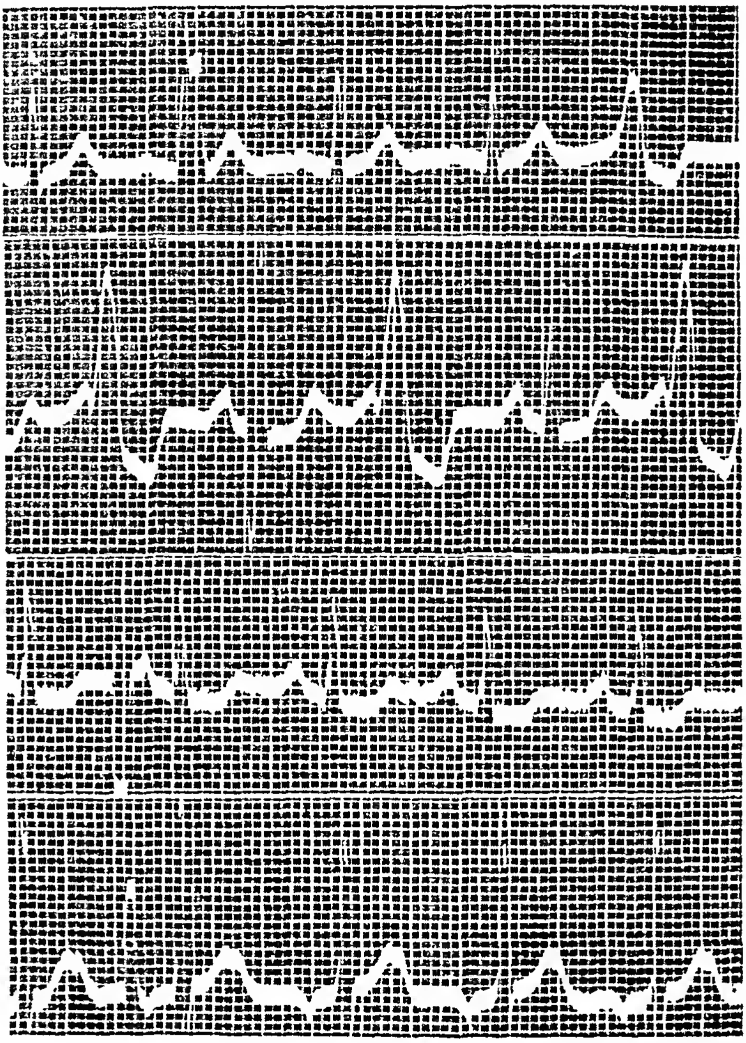


Fig. 4.—Case 3. Description in text.

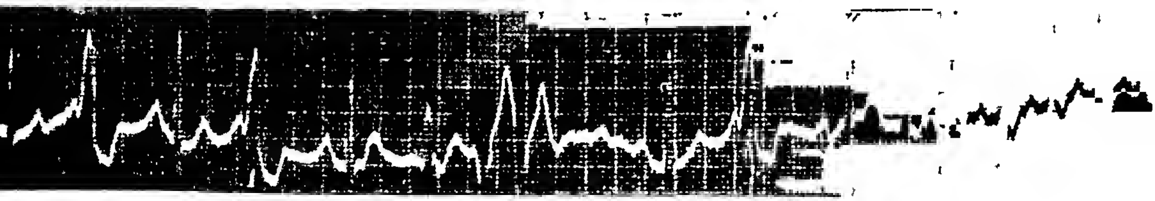


Fig. 5.—Case 3. Description in text.

Case 4.—This patient was 26 years old when he first came under observation by one of us (R. W. R.) in October, 1939. There was no history of vascular disease in his family. He had not had rheumatic fever, syphilis, or hypertension. His chief complaint was of frequently recurring attacks of palpitation for five months. The attacks were usually short in duration, lasting only a few minutes, but recurred almost daily. There were no symptoms of heart failure or angina.

On physical examination, his blood pressure was 125/70. His heart was of normal size, the rhythm was regular, and no murmurs were heard. The retinal vessels and peripheral arteries were normal. The urine, blood, and Kahn reaction were negative. The sedimenta-

On examination, his blood pressure was 150/110. The peripheral arteries were norma. The fundi showed no evidence of retinal vascular disease. The heart was normal size. Th heart rhythm was regular and no murmurs were heard. The heart size was normal on roent genologic examination. The blood and urine were normal. The blood nonprotein nitroge was 35 mg. per cent, and the phenolsulfonphthalein excretion, 75 per cent. His urine concen trated to 1.024 and diluted to 1.002. The sedimentation rate was 4 mm. (Westergre method), and the blood Kahn reaction was negative. An excretion pyelogram was normal An electrocardiogram (Fig. 2) showed a short P-R interval, of 0.10 to 0.12 second, and long QRS interval, of 0.12 second. An unusual feature of this case was inversion of th P waves in Lead III. The P waves are supposedly upright in all leads in this syndrome Subsequent tracings were identical with this one.

This patient was a physician. He did not have attacks of tachycardia, so that h was not disabled by this syndrome. He was reclassified on a limited duty status, con fined to the continental United States because of the hypertension, and not because o his electrocardiogram.

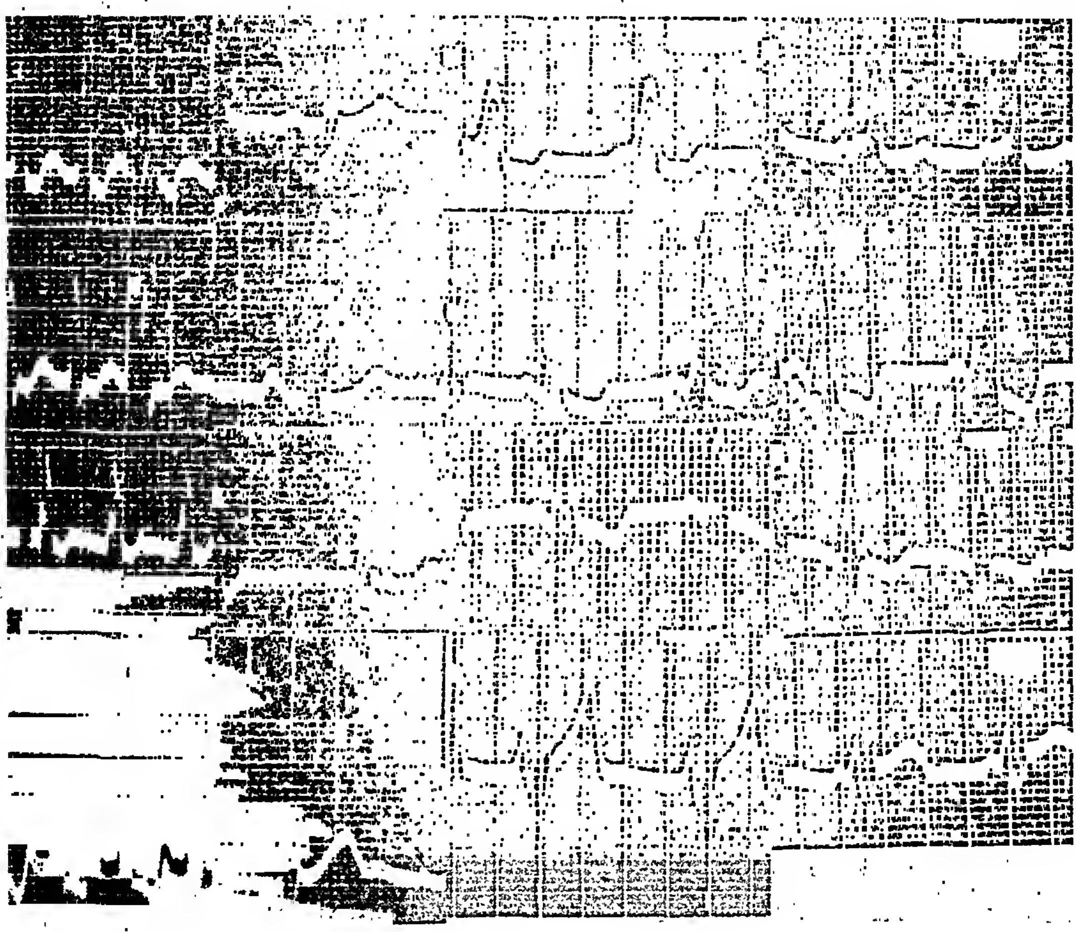


Fig. 3.—Case 3. Description in text.

Case 3.—This patient was a 29-year-old, white, male officer. There was no history of vascular disease in this patient's family. He had not had rheumatic fever, chorea, syphilis, or hypertension. His chief complaint was of recurrent attacks of palpitation during the preceding year. The attacks began suddenly, lasted several hours each time, and were relieved by lying down, bending over, or holding his breath.

On physical examination, his blood pressure was 110/68. The retinal vessels and peripheral arteries were normal. Examination of the heart was negative. The urine, blood, and Kahn reaction were negative. The sedimentation rate was 2 mm. (Westergren method). The blood nonprotein nitrogen was 31 mg., and the sugar, 78 mg., per cent. The heart size was normal on roentgenologic examination. An electrocardiogram (Fig. 3, *a*), taken Oct. 30, 1943, showed auricular tachycardia, with a rate of 180. Fig. 3, *b* shows a normal tracing, with a P-R interval of 0.20 second and a QRS interval of 0.08 second; this was recorded Dec. 7, 1943. Fig. 3, *c* shows the characteristic short P-R interval (0.09 second) and long QRS interval (0.14 second). Forty minutes after 1/75 grain of atropine subcutaneously, the QRS interval was shortened slightly in Lead I (Fig. 3, *d*). Fig. 4

tion rate was 4 mm. (Westergren method). The blood nonprotein nitrogen was 32 mg., and the sugar, 84 mg., per cent. The blood Kahn reaction was negative. The heart was of normal size on roentgenologic examination. An electrocardiogram (Fig. 6, *a*) taken Oct. 16, 1939, showed the characteristics of this syndrome, with a P-R interval of 0.10 second and a QRS interval of 0.12 second. Frequent tracings since then have been the same. However, a normal tracing was obtained Nov. 2, 1941 (Fig. 6, *b*), with a P-R interval of 0.18 second and a QRS interval of 0.08 second. On July 21, 1942, a supraventricular tachycardia, with a rate of 185, was recorded (Fig. 6, *c*). Another tracing, taken Sept. 2, 1942, still showed the electrocardiographic features of this syndrome (Fig. 6, *d*).

The patient had daily attacks of tachycardia, even when he was taking quinidine. He would therefore be unable to qualify as a soldier in the Army. He would in all probability be disqualified because of the disability produced by his attacks of tachycardia, and not because of the bizarre electrocardiogram.

CASE 5.*—This patient was an 18-year-old white girl. The past and family histories were negative. The patient had never had an attack of paroxysmal tachycardia or other symptoms referable to her heart. On Feb. 15, 1944, she had a sore throat. Two days later she experienced migrating joint pains, malaise, erythema nodosum, and fever.

On examination, her blood pressure was 116/68. The temperature was 102° F. The peripheral arteries were normal. The fundi showed no evidence of retinal vascular disease. The heart was of normal size. The heart rhythm was regular, and a soft systolic murmur was heard at the pulmonic area. The heart was of normal size on roentgenologic examination. The leucocyte count was 13,000, and the sedimentation rate, 84 mm. (Wintrobe method). The urine and the blood Kahn reaction were negative. An electrocardiogram (Fig. 7) showed the short P-R interval and long QRS interval characteristic of this condition. Subsequent tracings were identical with this one. The joint pains, fever, and erythema nodosum responded promptly to 20 grains of aspirin four times daily. There were no complications during her convalescence from rheumatic fever.

This was a case of rheumatic fever in a patient with the Wolff-Parkinson-White syndrome. The P-R interval did not become prolonged during the course of the rheumatic fever.

DISCUSSION

There were a few unusual features in these cases. It is characteristic for the P waves to be upright in the conventional leads. In Case 2, the P waves were diphasic or inverted. In Case 3 there was the unusual feature of normal beats, ventricular premature beats, and premature beats of the Wolff-Parkinson-White type leading into paroxysmal auricular tachycardia. In Case 3, also, normal beats alternated with premature beats which were identical with the beats of the Wolff-Parkinson-White type observed at other times in this patient, occurring as a bigeminy.

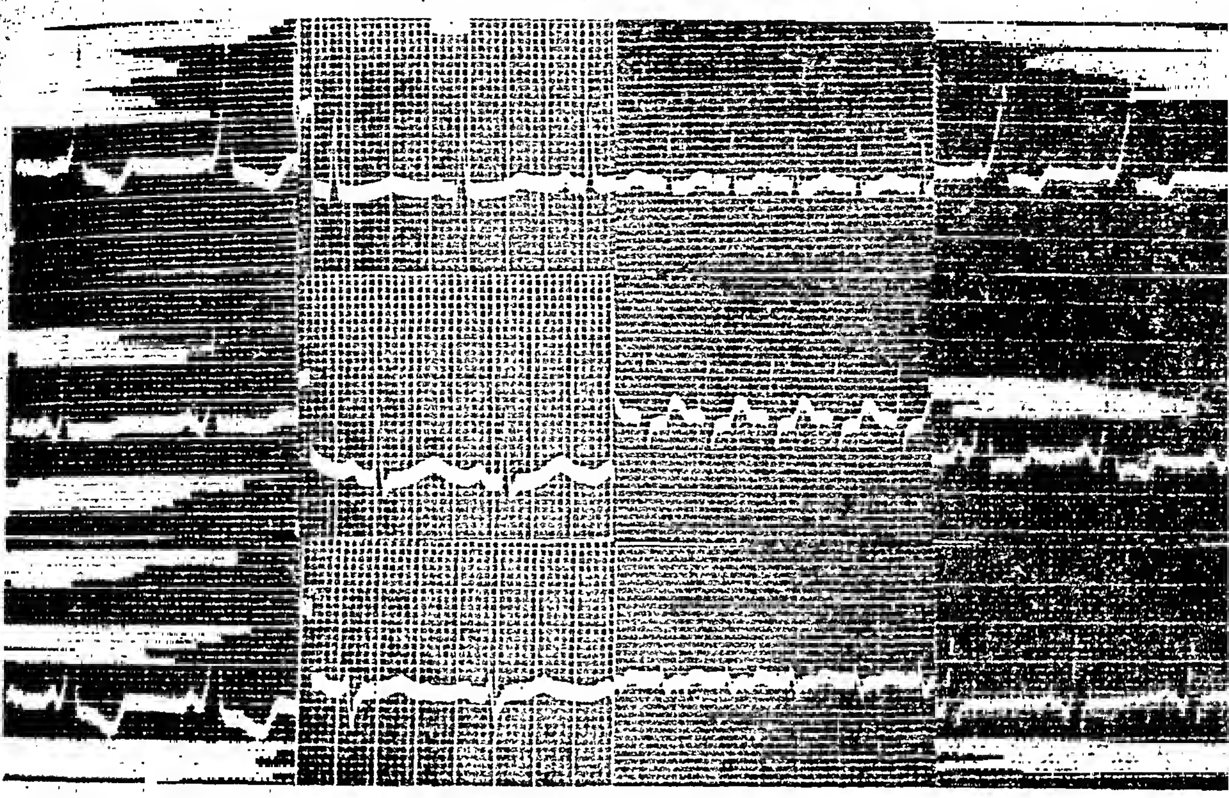
This syndrome is being recognized with increasing frequency. If there is no associated heart disease, the condition is apparently benign. If the patients are disabled by it, it is because of the associated attacks of paroxysmal tachycardia, and not the result of the bizarre electrocardiogram.

SUMMARY

Five cases of the Wolff-Parkinson-White syndrome have been presented, with comments upon some unusual features encountered. These patients may be able to perform useful service in the Army if they are not incapacitated by frequent attacks of paroxysmal tachycardia.

We wish to express our appreciation to Dr. S. A. Levine, of Boston, for his aid in interpreting some of the electrocardiograms. We are indebted to Colonel James S. Sweeney, Chief of the Medical Service at Bushnell General Hospital, for many helpful suggestions and the editing of this paper.

*We are indebted to Dr. J. C. Hayward of Logan, Utah, for permitting us to include this case in our series.



a. *b.* *c.* *d.*

Fig. 6.—Case 4. Description in text.

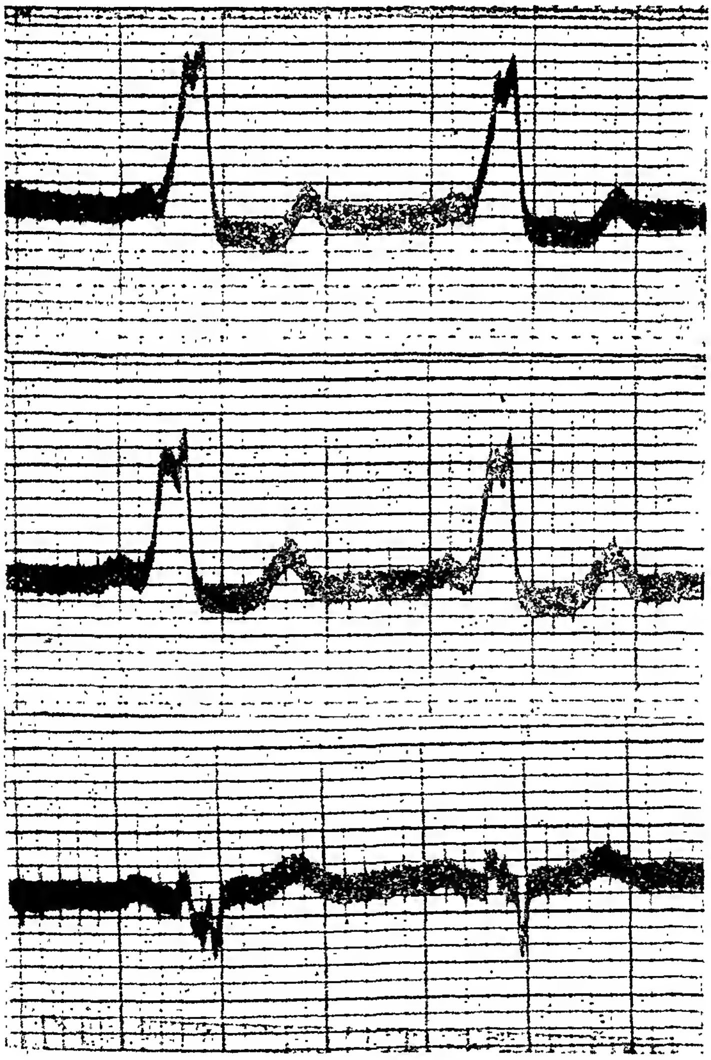


Fig. 7.—Case 5. Description in text.

TABLE I. COMPARISON OF MORTALITY IN CASES IN WHICH AURICULAR FIBRILLATION DISAPPEARED AND IN THOSE IN WHICH IT PERSISTED

	MORTALITY (%)
1,247 (whole group)	51.5
84 (with auricular fibrillation)	79.8
29 (in which arrhythmia disappeared)	58.6
55 (in which arrhythmia persisted)	89.4

TABLE II. RELATION OF TIME OF DEVELOPMENT OF AURICULAR FIBRILLATION TO THE DISAPPEARANCE OR PERSISTENCE OF THE ARRHYTHMIA

RELATION TO TIME OF MYOCARDIAL INFARCTION	AURICULAR FIBRILLATION		MORTALITY
	DISAPPEARED	PERSISTED	
8 (preceded)	1	7	99.0
41 (coincident)	1	40	81.8
35 (followed)	27	8	72.0

was only slightly increased. In the 55 cases in which it persisted, the death rate was markedly increased. The persistence was apparently the most important factor about the arrhythmia which influenced mortality. Persistence of auricular fibrillation was found to be correlated both with the time of onset of the arrhythmia and with the degree of pre-existing cardiac damage (Table II). In nearly all cases in which the auricular fibrillation preceded or coincided with the onset of the myocardial infarction, the arrhythmia persisted, whereas, in nearly three-fourths of those in which the auricular fibrillation occurred after myocardial infarction, the arrhythmia disappeared.

COMPARISON OF PERSISTENT GROUP WITH TRANSIENT GROUP (TABLE III)

The group with persistent auricular fibrillation showed evidence of marked pre-existing cardiac damage. In this group, as contrasted with the group in which the arrhythmia disappeared, twice as many gave histories of signs and symptoms of previous cardiovascular disease, such as hypertension, dyspnea, and edema (83.6 per cent as compared with 41.3 per cent). One-half gave histories or had necropsy evidence of previous infarcts, and nearly three-fourths had congestive failure. A surprising discovery was the number who died with clinically suspected systemic emboli. Nearly one-third of the deaths in the group with persistent auricular fibrillation were due to such emboli, as contrasted to only one-ninth in the group in which the arrhythmia disappeared. The conversion to sinus rhythm was not as productive of emboli as was the persistence of the arrhythmia.

Clinically suspected embolism in the greater circulation, only, was considered. Pulmonary embolism may often arise from peripheral venous thrombi, but sudden hemiplegia or sudden arterial obstruction in an extremity, if due to embolism, can arise only from the left side of the heart, save in paradoxical embolism due to anomalies of the cardiac septa.

TABLE III. COMPARISON OF PERSISTENT GROUP WITH TRANSIENT GROUP

AURICULAR FIBRILLATION	AVERAGE AGE (YRS.)	PREVIOUS CARDIOVASCULAR DISEASE	PREVIOUS INFARCTS	CONGESTIVE FAILURE	SYSTEMIC EMBOLI	DEATHS
Transient (29)	66	12 (41.3%)	2 (6.9%)	7 (24%)	2 (11%) (of deaths)	17 (58.6%)
Persistent (55)	68	46 (83.6%)	30 (52.6%)	41 (71.8%)	15 (29.4%) (of deaths)	51 (89.4%)

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THE PROGNOSTIC SIGNIFICANCE OF AURICULAR FIBRILLATION IN ASSOCIATION WITH MYOCARDIAL INFARCTION

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AURICULAR fibrillation is infrequently associated with myocardial infarction. Prognostically, it has not been regarded as a serious complication alone, but rather as a reflection of an advanced degree of cardiac failure. It has been regarded as usually transient, requiring no specific consideration. Because of its infrequency, no large series of cases has been analyzed. Master, Dack, and Jaffe[1] found 22 instances among 300 patients with myocardial infarction (7.3 per cent); Rosenbaum and Levine[2] found 25 among 208 patients (12 per cent), and Rathe,[3] 35 among 274 patients (12.7 per cent).

MATERIAL

We have studied 84 patients with auricular fibrillation; this occurred in a group of 1,247 patients with myocardial infarction who were admitted to the Los Angeles County General Hospital, an incidence of 7.7 per cent. This paper concerns itself only with the prognostic significance of the arrhythmia in these cases. The diagnosis of myocardial infarction was accepted only when the history and electrocardiogram were typical. Auricular fibrillation was diagnosed only when confirmed by electrocardiograms. Probably many cases of transient fibrillation, with no tracings, were overlooked. Therefore, the figures do not actually represent the incidence of the arrhythmia in its transient form. They should, however, represent the incidence of the persistent form in this group. Contrary to expectations, auricular fibrillation was found to be persistent in a large number of cases. In 29 instances the arrhythmia disappeared; in 55 it persisted.

MORTALITY RATES

The mortality among the 1,247 patients with myocardial infarction during their hospitalization (about one month) was 642, a rate of 51.5 per cent (Table I). The 84 patients with auricular fibrillation had a definitely higher death rate. In the 29 cases in which the arrhythmia disappeared, the mortality rate

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Received for publication July 16, 1944.

by the effect of auricular fibrillation complicating myocardial infarction in the absence of congestive failure. Of two groups with myocardial infarction, but no congestive failure and no known previous infarcts, in which the presence of auricular fibrillation in one group was the only variable, both the mortality rate and the incidence of systemic emboli were markedly increased in the one in which the arrhythmia was present. Persistent auricular fibrillation, therefore, was a hazard whether it was imposed upon previously damaged hearts or upon previously undamaged hearts.

SUMMARY OF OBSERVATIONS

1. The mortality rate among patients with myocardial infarction plus auricular fibrillation was much higher than in a group without auricular fibrillation.

2. Prognostically, if the auricular fibrillation disappeared in one day, the mortality rate was slightly increased; if it persisted longer than one day, the mortality rate increased markedly.

3. If no reversion to sinus rhythm occurred, death ensued in 89 per cent. One-third of the deaths were due to clinically recognized systemic emboli.

4. Persistence of the arrhythmia could be correlated with pre-existing cardiac damage.

5. Cardiac damage, however, was not the sole cause of the high mortality rate and high incidence of embolism.

6. Auricular fibrillation increased the mortality rate and incidence of embolism, regardless of whether congestive failure was or was not present.

7. Whether or not auricular fibrillation was found in the first electrocardiogram was a fairly reliable way of predicting whether the arrhythmia would be persistent or transient. In only eight of the 55 cases in which auricular fibrillation was found in the first tracing did the arrhythmia disappear, whereas, in 27 of 35 in which the arrhythmia followed myocardial infarction, sinus rhythm returned. If the auricular fibrillation definitely followed myocardial infarction, the prognosis was about average if it disappeared in one day or less; but if it lasted over one day, the prognosis was much worse because then the arrhythmia persisted in about one-third. The worst prognosis was among those whose auricular fibrillation was known to have existed before (99 per cent mortality, with 57 per cent dying of systemic embolism), and among those who had had a previous infarct (96 per cent mortality, with 30 per cent systemic embolism). Only congestive heart failure with enlargement of the liver and edema of the ankles was considered.

RELATION TO LOCATION OF INFARCT

There was no correlation of the auricular fibrillation with the location of the infarct. Wood, Wolferth, and Bellet[1] found a high incidence of auricular fibrillation in association with lateral infarction of the left ventricle. Thomson

TABLE VI. LOCATION OF INFARCTS AT NECROPSY IN FIFTY-ONE CASES OF MYOCARDIAL INFARCTION AND AURICULAR FIBRILLATION

	NO.	%
Left lateral wall (recent)	8	16
Left lateral wall (old) plus posterior infarction (recent)	3	6
Interventricular septum	3	6
Anterior and posterior (combined)	2	4
Posterior	14	28
Anterior	21	42

Persistent auricular fibrillation, therefore, produced a very high death rate (89.4 per cent). In 85 per cent, the arrhythmia appeared in the first electrocardiogram and was usually associated with congestive failure. One-third of the deaths were due to systemic arterial emboli.

THE EFFECT OF MEDICATION

Although auricular fibrillation tended to disappear in the majority of patients who received quinidine alone, and to persist in the majority of patients who received digitalis alone (Table IV), the effect of the medication was not conclusive. Quinidine alone was used for patients with little pre-existing heart damage, in many of whom the arrhythmia was recent and might spontaneously have disappeared, whereas digitalis alone was used for those with marked pre-existing damage, in many of whom the arrhythmia was already established. Digitalis is not used to terminate auricular fibrillation, whereas quinidine is. It is impossible to predict, therefore, whether or not the auricular fibrillation would have disappeared anyway in those cases in which quinidine apparently stopped the arrhythmia. It is also impossible to predict what the effect upon the arrhythmia would have been had quinidine been given in addition to digitalis in those cases in which the auricular fibrillation persisted.

TABLE IV. RELATION OF TYPE OF MEDICATION TO THE DISAPPEARANCE OR PERSISTENCE OF AURICULAR FIBRILLATION

MEDICATION	NUMBER	NUMBER DISAPPEARED	NUMBER PERSISTED
None	17	5	12
Quinidine alone	11	9	2
Digitalis alone	44	6	38
Digitalis and quinidine	12	9	3
Total	84	29	55

THE EFFECT OF PRE-EXISTING CARDIAC DAMAGE

Since marked pre-existing cardiac damage was so closely correlated with persistent auricular fibrillation, one must ask whether the damage alone was responsible for the high mortality and the high incidence of embolism. Can one ignore the arrhythmia, per se, in the prognosis, and predict the outcome upon the basis of the cardiac damage alone? If so, patients with myocardial infarction and congestive failure, but with no auricular fibrillation, should show approximately the same mortality rate and incidence of embolism as a similar group in which auricular fibrillation was the only other complication (Table V).

The incidence of embolism was much lower, however, when no auricular fibrillation occurred (7 per cent as compared with 34 per cent), indicating that the arrhythmia increased the hazard of embolism. This was further suggested

TABLE V. MORTALITY AND CLINICALLY RECOGNIZED EMBOLISM (SYSTEMIC) IN MYOCARDIAL INFARCTION

(Effect of Congestive Failure and Auricular Fibrillation)

PATIENTS WITH MYOCARDIAL INFARCTION	MORTALITY (%)		PERCENTAGE OF SYSTEMIC EMBOLI		NUMBER OF CASES	
	WITHOUT AURICULAR FIBRILLATION	WITH AURICULAR FIBRILLATION	WITHOUT AURICULAR FIBRILLATION	WITH AURICULAR FIBRILLATION	WITHOUT AURICULAR FIBRILLATION	WITH AURICULAR FIBRILLATION
With congestive failure	83.0	89	7	34	85	48
No congestive failure—no previous infarcts	43.4	66	4	16	76	36

ventricular rate and by increasing the possibility of fatal systemic emboli would seem imperative. The factors to be considered are complex, and will be dealt with in another study.

CONCLUSIONS

Auricular fibrillation in association with myocardial infarction in a series of eighty-four patients at the Los Angeles County General Hospital was a hazard as regards both mortality rate and the incidence of systemic emboli.

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GASTROINTESTINAL SYMPTOMS OF PROGRESSIVE MYOCARDIAL DISEASE

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STATEMENTS can be found in medical literature to the effect that gastrointestinal symptoms are of common occurrence in primary heart disease, and that these symptoms may largely overshadow the more typical symptoms of heart failure. Thus, in 1892, Osler[1] made the observation that "cases of cardiac insufficiency which do badly and fail to respond to digitalis are most often those in which nausea and vomiting are prominent symptoms." Likewise, Herrick,[2] in his original article on the clinical features of coronary occlusion, remarked that "nausea and vomiting with belching of gas are quite common." Prior to the publication of Herrick's classic paper, and indeed even up to the present writing, the acute phase of coronary occlusion has often received the misnomer of "acute indigestion."

In spite of these and other isolated instances, it is rather remarkable that so little attention has been directed to the gastrointestinal symptoms of congestive heart failure from the point of view of diagnosis, prognosis, or treatment, and the rather meager experimental work in this field has not been given

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Received for publication July 27, 1944.

and Feil[5] recently published a similar report. In fifty-one of our patients with auricular fibrillation, necropsy revealed no significantly higher incidence of lateral wall infarctions than is found in a group without auricular fibrillation. The percentage distribution of the location of the infarction was much the same as in patients with no auricular fibrillation (Table VI).

CAUSE OF AURICULAR FIBRILLATION

What causes auricular fibrillation to appear in association with myocardial infarction? Auricular anoxemia and vagal stimulation are apparently the important factors in its production in the experimental animal.[6] Congestive failure and auricular distention are apparently important to the extent that they induce auricular anoxemia, but neither is essential for the production of auricular fibrillation. Vagus stimulation alone has produced auricular fibrillation in the dog.[7] Apparently, in coronary artery insufficiency, there is hypersensitivity to vagal stimuli, as suggested by the increased sensitivity of the carotid sinus reflex.[8] The production of auricular fibrillation would seem to be determined by the degree of vagal activity, the degree of auricular anoxemia, and the individual susceptibility of the patient. A higher percentage should therefore be found among the patients with congestive failure, and the auricular fibrillation should persist longer. This was found to be true. Although it was impossible in most instances to ascertain which was the precursor, congestive failure or auricular fibrillation, they were associated in forty-eight instances. In these cases the arrhythmia usually persisted. Congestive failure was not necessary to precipitate the arrhythmia, however. Auricular fibrillation occurred in thirty-six cases without congestive failure. In most of these the arrhythmia disappeared.

DISCUSSION

This series was surprising because of the large number whose auricular fibrillation persisted until death. Forty-seven of the fifty-five patients with persistent auricular fibrillation showed the arrhythmia in the first tracing, so that it was impossible to know in how many it existed before the onset of myocardial infarction. Levine[9] believes that myocardial infarction occurs rarely in patients with persistent auricular fibrillation, but in eight of our cases the arrhythmia had been demonstrated in previous tracings and out-patient examinations. In how many of the others it existed prior to the onset of infarction is unknown.

It is apparent that severe, long-standing cardiac damage was the cause of persistent auricular fibrillation. Despite the severity of the underlying damage, however, the data would suggest that the arrhythmia was definitely an additional hazard, increasing the death rate in general, and systemic embolism, in particular, over and above that which would result from the cardiac damage alone.

The concept that auricular fibrillation is not a significant prognostic hazard when associated with myocardial infarction has been based upon the premise that it is transitory, and that it is the associated shock and heart failure, rather than the arrhythmia, which is dangerous. The above series demonstrates that auricular fibrillation may not be a serious prognostic factor if it is transitory, but that the persistent form is not necessarily uncommon, and constitutes a definite prognostic hazard. The elimination of an ectopic rhythm which increases the load upon a badly damaged heart by increasing

CASE REPORT

A. R., a 44-year-old white merchant, was admitted to the private medical service of the North Carolina Baptist Hospital with an illness of about two months' duration. He had been known to have hypertension for approximately ten years, and his family physician had found his blood pressure as high as 240/140 on frequent occasions. He had, however, been active and relatively free of symptoms until his present illness. He had complained of slight dyspnea and of "twinges of pain in the chest" on exertion for several years, but these were never severe, required no medication, and produced no disability.

On Jan. 28, 1943, two months prior to admission, the patient awakened early in the morning with a feeling of nausea which became progressively more severe. This was accompanied by a sense of substernal oppression, and he vomited several times. He complained chiefly of the nausea and vomiting, but was moderately dyspneic and stated that his physician noted a fall in his blood pressure.

The diagnosis of coronary occlusion was determined upon, and the patient remained in bed for the next three weeks, after which he gradually resumed his work in his store. During his convalescence he continued to complain of severe nausea which was relieved only by vomiting. These symptoms occurred as often as three to five times a day; the vomitus was yellowish green, without blood. He was receiving no digitalis at this time.

He showed gradual improvement and returned to work, but three weeks prior to admission he was again awakened during the night by severe nausea, vomiting, and a sensation of constriction in his chest. He was taken to another hospital, where he remained until being transferred to the Baptist Hospital. In the interim he had been given digitalis and aminophylline without improvement. Tachycardia at a rate of 140 per minute was noted. This persisted and resisted the above therapy, as did the nausea and vomiting.

The family history revealed that one brother had died of hypertension, one brother had hypertension and was living, and one son, aged 20 years, had been rejected by the Army Medical Corps because of high blood pressure.

Physical Examination.—On March 30, 1943, the date of admission, the patient's temperature was 36.8 C. (98 F.), his pulse rate, 140 per minute, and his respirations, 28 per minute. The systolic blood pressure was 158 mm. Hg, and the diastolic pressure was 148, with complete disappearance of sounds at 135 mm. Hg, resulting in a pulse pressure of only 10 mm. of mercury.

The patient was a heavy-set, ruddy-faced male, appearing chronically ill. His breathing was of the Cheyne-Stokes variety, and the neck veins were moderately distended. Ophthalmoscopic examination revealed marked narrowing of the arterioles, with advanced arteriovenous nicking and mild papilledema. There was no hemorrhage or exudation. The chest was symmetrical, with fair expansion; there were diminished breath sounds in both bases, and also a few scattered, moist, crackling râles. The cardiac dullness was remarkably increased and extended to the anterior axillary line in the fifth left intercostal space. The entire precordium appeared to shiver during systole, and the apex impulse was not well localized. The sounds were clear and of moderate intensity, and a presystolic gallop rhythm was heard, best at the apex. The radial pulses were of small volume, equal, and regular.

The abdomen was pendulous and showed no spasm or tenderness. Questionable shifting dullness was noted. The liver was palpable about 4 cm. below the costal margin and was quite tender.

There was no edema of the extremities, scrotum, or over the sacrum. Neurologic examination was negative. Rectal examination revealed no lesion.

Accessory Clinical Data.—The specific gravity of the urine was 1.029. There was a faint trace of albumin, but no sugar, and the microscopic examination showed occasional hyaline and granular casts. Erythrocyte counts on two occasions were 5.9 and 5.2 million, and the hemoglobin was 17.5 and 15 Gm. per 100 c.c. of blood (Sahli). The total and differential leucocyte counts were not remarkable. The blood nonprotein nitrogen varied from 30 mg. per 100 c.c. on admission to 47 mg. per 100 c.c. two days prior to death. The blood sugar on admission was 97 mg. per 100 cubic centimeters. The total serum protein two weeks after admission was 5.4 Gm. (albumin, 3.5 Gm., globulin, 1.9 Gm., albumin-globulin ratio, 1.8:1). At this time the icterus index was 25 units. The blood chlorides were 73 meq. per liter one week after admission, but, after intravenous fluid therapy, were 94 meq. per liter. The blood cholesterol was 273 mg. per 100 c.c., and the blood Kahn reaction was negative.

The electrocardiogram revealed normal sinus rhythm at a rate of 136, and slight left axis deviation. The P-R interval was 0.16 second, and QRS, 0.06 second; $S\text{-}T_1$ and $S\text{-}T_4$

full clinical application or led to more illuminating studies. It is, therefore, our purpose to review briefly the literature on nausea and vomiting as manifestations of severe cardiac disease, outlining some current concepts of the underlying pathologic physiology, and to present a case of progressive myocardial failure in which gastrointestinal symptoms dominated the clinical picture and resisted all therapy; their steadily increasing severity paralleled the fatal course of events.

Levine[3] states that there are many instances of congestive heart failure in which nausea, abdominal distress, and often vomiting occur. Harrison[4] reports that occasionally these symptoms occur in patients with chronic congestive failure and in myocardial infarction; in the former they are ascribed to venous congestion of the liver and stomach. Christian[5] and Tice[6] also make brief references to the occurrence of nausea and vomiting in heart disease. The fact that these various authors recognize that these symptoms are at least occasionally a part of the clinical picture of chronic heart failure leads one to conclude that their occurrence is not uncommon, although no statistical data are available to support this belief.

That the presence of nausea and vomiting does not necessarily imply a primary disturbance of the digestive tract is all too frequently lost sight of by the physician, and perhaps accounts for the relative scarcity of clinical correlation between primary cardiac disease and gastrointestinal symptomatology. The common fallacy of ascribing these symptoms directly to the digestive tract is evident when one recalls the pharmacologic action of such drugs as digitalis and apomorphine. Hatcher and Weiss[7] showed experimentally that the emetic effect of digitalis bodies was exerted by reflex action directly from the heart itself. They further concluded that the heart proper is frequently the seat of the vomiting reflex induced by primary disease of this organ.[8, 9] This concept is supported by the work of Sutton and King,[10] who found that, in conscious dogs, traction upon a ligature passed loosely about a coronary artery and brought out through the thoracic wall was followed by vomiting and apparent nausea. It was further demonstrated by these two groups of authors, who were working independently, that the afferent arc of this reflex is chiefly by way of the sympathetics, and, in part, probably by the vagi to the vomiting center in the region of the sensory nuclei of the vagi near the floor of the fourth ventricle. The efferent pathways of the reflex of nausea and vomiting are well understood and will not be discussed here. Further interrelationships of the heart and stomach have been noted by Manning, Hall, and Banting,[11] who found marked congestion, with hemorrhages, in the stomach and duodenum, along with infarctions of the myocardium, after repeated stimulation of the vagus nerve in dogs. Gilbert, Fenn, and LeRoy[12] produced reflex coronary vasoconstriction in dogs by initiating vagal stimulation in the gastrointestinal tract. Likewise, Levy and Boas[13] showed that patients with peptic ulcer who later developed angina pectoris had their angina in the form of epigastric pain, often simulating the pain of peptic ulcer as experienced previously, but with the typical causal factors of exertion and emotion.

The studies discussed above may be summarized as follows: (a) Disorders of the heart may produce reflex disturbances of the stomach, and vice versa. (b) Nausea and vomiting are not uncommon symptoms of cardiac disease, especially disease resulting from inadequate coronary flow. (c) These symptoms may, under certain conditions at least, be induced reflexly from the heart itself. The following case seems to illustrate these several points.

more extensive fibrosis was seen in the posterior wall and in the interventricular septum. Typical arteriolar sclerosis, with an occasional area of thrombosis, was found. The coronary arteries showed all degrees of arteriosclerosis, with luminal narrowing and finally thrombosis.

DISCUSSION

One is impressed with several features of this case which, in our experience, are not infrequent as sequelae of coronary thrombosis. These features are essentially myocardial infarction, manifested mainly by protracted nausea and vomiting. After this there was progressive cardiac insufficiency over a period of approximately two months, and the symptoms were predominantly gastrointestinal in nature and resisted all therapy.

Interesting, too, were the persistently high diastolic blood pressure and low pulse pressure, which led one to suspect pericardial effusion or constrictive pericarditis. Furthermore, the patient's entire course was characterized by evidence of "forward failure," and only terminally was there much evidence of congestive failure.

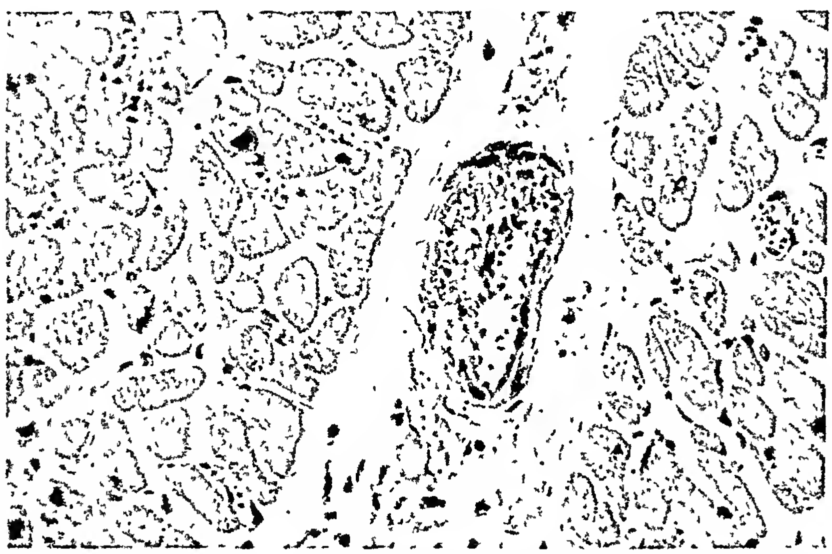

Fig. 1.—A section through apparently normal mycocardium. In the center of the photomicrograph is a small artery which shows localized thickening of the subendothelial connective tissue.

The usual causes of vomiting and nausea in a case of congestive heart failure are: (1) drugs, (2) visceral congestion, (3) vitamin deficiencies, (4) stimulation of the vomiting center by metabolites, as in uremia, and (5) extensive myocardial damage, as with the myocarditis of acute rheumatic fever. In the case presented here the nausea and vomiting were not produced by drugs such as digitalis or opiates, for the symptoms occurred prior to their administration and persisted after their discontinuance. Nor can these symptoms be attributed to visceral congestion, for at necropsy the viscera, except for the liver, showed only minimal congestion, and, indeed, the nausea and vomiting were prominent features even before the congestive phenomena were observed. The failure to improve after parenteral vitamin therapy apparently excludes vitamin deficiencies as causes of the nausea and vomiting. However, Smith and Furth[7] have reported several cases of vitamin deficiency in which the clinical course closely paralleled this case, and this raises the question whether this case may also have been an instance of chronic deficiency of vitamin B complex, as they suggest. There was no history of any such lack in this case, how-

were depressed; S-T_3 was elevated; T_1 and T_4 were upright; and T_2 and T_3 were inverted. Diagnosis: Sinus tachycardia. The record suggested myocardial disease with fairly recent myocardial infarction, probably of the posterior type.

Fluoroscopic examination of the chest showed marked cardiac enlargement due to hypertrophy and dilatation, without characteristic configuration. The amplitude of the cardiac contractions was greatly reduced. The fluoroscopic examination was repeated three weeks after admission, but no change was seen. Gastrointestinal roentgenologic studies two weeks after admission were negative. The basal metabolic rate +27 per cent. The venous pressure soon after admission was 30 cm. of saline. The circulation time (arm-to-tongue, using calcium gluconate) was 45 seconds, and the vital capacity was 2.25 liters.

Clinical Course.—The patient was given digitalis and, later, squill (Urginin). He continued to complain constantly of severe nausea, and vomited frequently. The pulse rate never fell below 116 per minute, and he continually had a pulse pressure of only 10 to 20 mm. of mercury.

On April 10, 1943, all oral medications except sedatives were discontinued without change in the patient's condition. On April 17, he began to show pitting edema over his sacrum, and, on April 19, of his ankles. Because there was evidence of ascites, abdominal paracentesis was performed; this yielded only 100 c.c. of thick yellow fluid, which congealed within fifteen minutes. The specific gravity of this fluid was 1.014.

The patient began to expectorate bright red blood on April 23, and, on April 25, his temperature rose to 38.5 C. The blood pressure had fallen slowly since admission, and was 116/100 at this time. The next day he complained of pain in the right side of his chest, and showed marked tenderness to percussion over the right hemithorax anteriorly from the costal margin to the precordium. Râles had been heard over the lower lobe of the right lung, and signs of consolidation appeared in that area. A diagnosis of infarction of the lung was made because of signs of consolidation plus marked tenderness over the area.[14] Salyrgan and aminophylline were given intravenously without effect.

Because of the persistent nausea and vomiting, fluids were given parenterally, with large amounts of thiamine hydrochloride and liver extract intramuscularly. The nausea and vomiting were constant complaints. At times the patient became quite irrational. Relief was obtained only by sedatives.

On April 27, 1943, he became unable to void, and catheterization was necessary. Edema had become severe, but the lungs were relatively clear except for the signs of consolidation in the lower half of the right lung.

On the morning of April 29, 1943, the patient's pulse became small and rapid, and the blood pressure was imperceptible. He was irrational, covered with cold clammy sweat, and presented a picture of peripheral and central circulatory collapse, with pulmonary edema. Only terminally did the patient develop any orthopnea; until then he was able to lie relatively flat in bed without respiratory distress. The pulmonary edema became more severe, and the patient died at noon on April 29, 1943.

The autopsy observations were as follows: The peritoneal and right pleural cavities contained, respectively, 1,350 and 700 c.c. of straw-colored, clear fluid with a specific gravity of 1.015. Several infarcts were found in the lower lobe of the right lung, and ante-mortem blood clots occluded the lumina of the pulmonary arteries which supplied these areas. The liver, which weighed 1,650 grams, was congested. The heart weighed 450 grams. The chambers of the right side were dilated, and the wall of the left ventricle was hypertrophied. The homogeneous gray color of the subendothelial tissue of the left ventricle was in striking contrast to the reddish-brown color of the inner surface of the right ventricle. A mural thrombus 2.5 cm. in diameter was attached to the left anterior wall, and the musculature in that area was softened and dark brown in color. Section of the left ventricular wall revealed a thin subendothelial zone and extensive patchy areas of fibrosis involving especially the interventricular septum and the posterior wall. Examination of the coronary arteries revealed numerous atherosclerotic plaques which had produced varying degrees of narrowing of the lumina of these vessels. The right main coronary artery contained a fresh thrombus which completely occluded its lumen 2 cm. from its orifice at the sinus of Valsalva.

On microscopic examination, the kidneys, adrenal glands, pancreas, and myocardium showed marked arteriolar sclerosis. The mural thrombus was in an early phase of organization. The subendothelial tissue of the myocardium was swollen and hyalinized. Focal areas of fibrosis of variable maturation, and acute and chronic inflammatory reactions were evidence of repeated occlusions of small branches of the coronary arteries. The older and

ever, and, in addition, the patient received enormous amounts of vitamin B complex intramuscularly, and thiamine hydrochloride in doses of 100 to 200 mg., intravenously, on many occasions.

Hatcher and Weiss[9] found that substances formed in the body in disease may raise the excitability of the vomiting center to a level where afferent impulses which are ordinarily of subliminal value may initiate the reflex. Since, however, vomiting is rare in cases of severe anoxia due to chronic pulmonary disease, as well as in those with severe "forward failure" due to constricted hearts, it seems unlikely that in this case the above mechanism was of major importance.

From the necropsy notes and photomicrographs (Figs. 1, 2, 3, and 4) it is apparent that the essential abnormalities were limited to the myocardium, and in this case we believe the protracted nausea and vomiting were due to the extensive myocardial disease per se, acting through the same mechanism which is responsible for the emesis produced by digitalis and which, as Hatcher and Weiss[7] have shown, is initiated by a reflex from the myocardium.

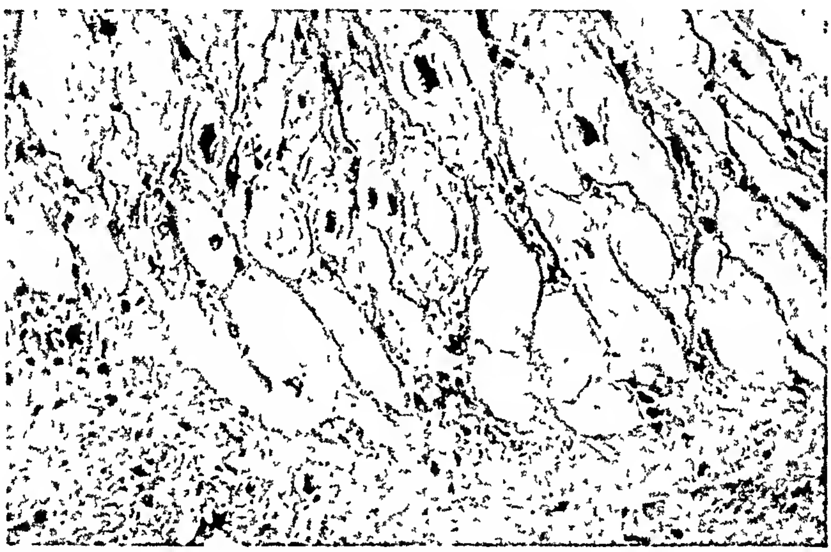

Fig. 4.—High-power photomicrograph showing acute myocardial degeneration.

Correlating the clinical and pathologic data, we assume that the following events took place: Initially, a patient with severe hypertension suffered coronary thrombosis from which he largely recovered. Subsequently, he developed another occlusion with a fall in blood pressure. Previously existing vascular disease and extensive myocardial damage combined to produce forward failure of the circulation brought about by the combination of deficient cardiac output, low arterial pressure, extremely low pulse pressure, myocardial anoxia due to low-grade coronary insufficiency, and further thrombosis of small coronary artery radicals. From this point a vicious cycle was set up, and the patient developed other smaller infarctions which led to still further coronary artery insufficiency. This combination of factors resulted in generalized myocardial anoxia. Finally, pulmonary infarctions developed which imposed an additional load on the badly weakened myocardium, resulting in terminal pulmonary edema.

It is our belief that such a slowly progressive cycle of events was the cause of the protracted gastrointestinal symptoms in this case; we further believe that the syndrome is not of infrequent occurrence, for the reports of other authors—for example, Smith and Furth[15]—are not unlike this case in many respects.

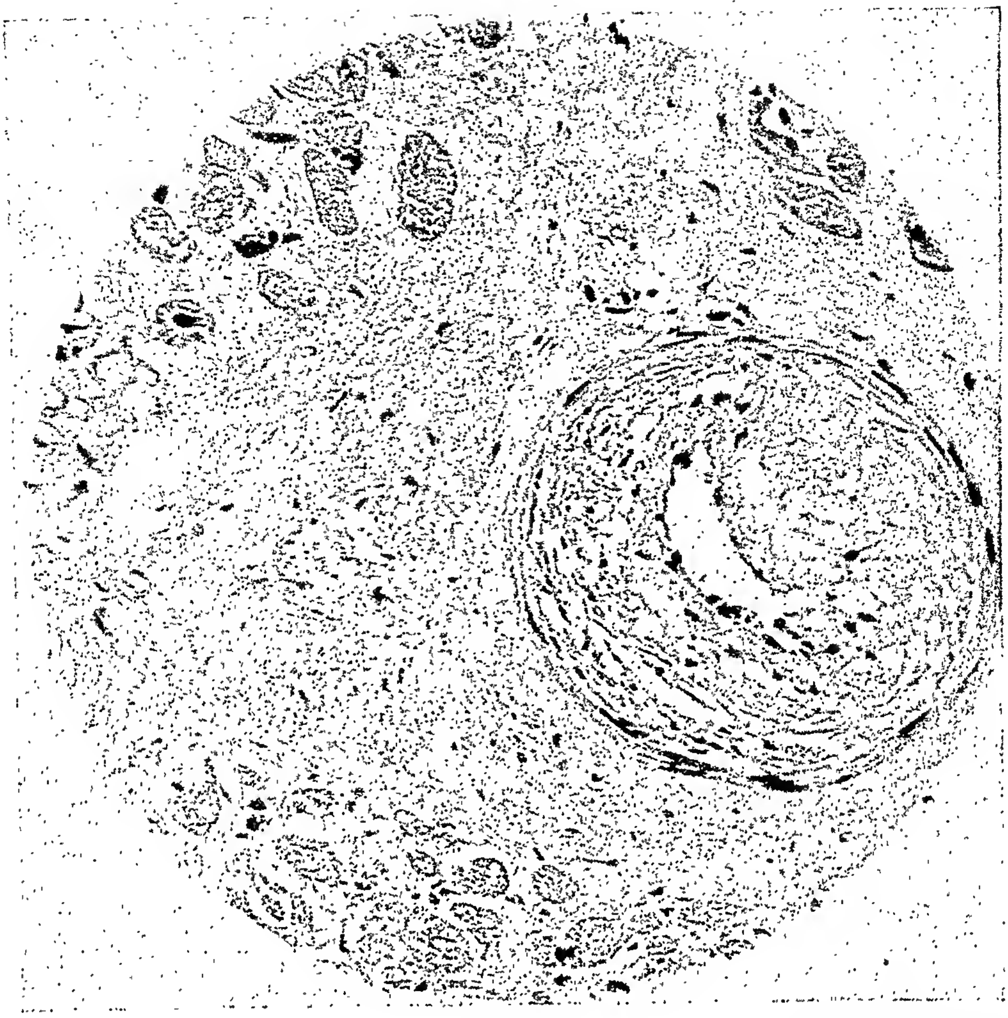

Fig. 2.—An area of myocardial scarring. At the edges of the photomicrograph, the cells are in varying stages of degeneration. The lumen of the small artery is almost completely obliterated by subendothelial connective tissue deposits.

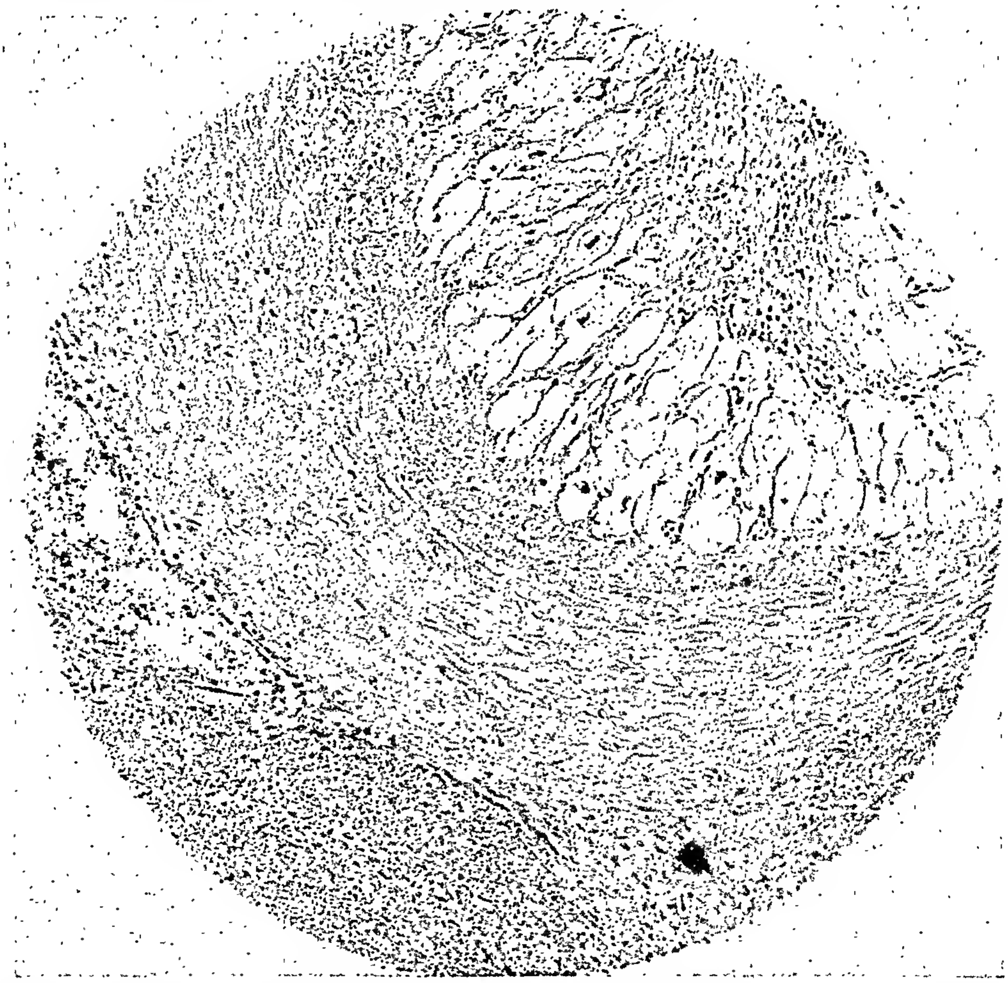

Fig. 3.—In this photomicrograph, made of a section through one of the myocardial infarctions, degenerating myocardial fibers are seen together with endocardial thickening and mural thrombosis.

CORONARY OCCLUSION IN INDUSTRY

A Study of Eighty-Four Cases With Reference to Subsequent Employability

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PURPOSE OF STUDY

There has been a definite unwillingness on the part of large industries to employ persons who are known to have arteriosclerotic heart disease or to have had myocardial infarction. This is evidenced by the employment criteria of the Eastman Kodak Company. Crain[1] states that, in 1934, this company held that a diagnosis of arteriosclerotic heart disease disqualified any man for employment. Although it is important that employers be properly safeguarded, it is equally important that persons who have recovered from myocardial infarction should be returned in so far as possible to a useful and productive position in society. Above all, they should not become dependent by reason of illness unless it is shown that the illness actually impairs their productive value. This is always important, particularly at the present time, when the armed forces are making a tremendous demand on man power, and industry must utilize all available workers.

More recently many industries have taken a less stringent view. This is in line with published studies indicating that satisfactory functional recovery frequently follows myocardial infarction.[1]

Although there are many impressions relating to the suitability or unsuitability of such persons for various types of work, there are few facts based on actual study of industrial performance. In a recent symposium on the workman's heart,[8] it was observed that the literature contained many generalities on the subject, but that the need was for a formula for physicians to work on.

This study was undertaken as a step toward providing such a formula.

The questions we seek to answer are: What proportion of persons who sustain coronary occlusion with myocardial infarction return to gainful employment? What sort of work do they do? How long do they do it? Why do they stop? If they don't return to work, why don't they?

MATERIALS AND METHOD

Eighty-four employees of the Kaiser shipyards, with a total of ninety-seven infarctions, were studied. No cases of myocardial infarction after Dec. 31, 1943, were included. Eleven patients had two separate myocardial infarctions, and one patient had three. The period of observation terminated April 20, 1944.

Cases for study were chosen by reviewing all of the electrocardiograms in the files of the Permanente Foundation Hospital. The occurrence of myocardial infarction was confirmed by subsequent perusal of the case histories.

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Presented at the Annual Meeting of the California Heart Association, Los Angeles, May 6, 1944, and the Annual Meeting of the Western Association of Industrial Physicians and Surgeons, Los Angeles, May 6, 1944.

Received for publication Aug. 2, 1944.

SUMMARY

The condition presented involves a patient who, after coronary occlusion, developed heart failure, the primary symptoms of which were nausea and vomiting, and in whom the significant pathologic changes were multiple areas of myocardial fibrosis. As a result of the experiences with this and other similar cases and a review of the literature, the following conclusions are drawn:

1. When nausea and vomiting are dominant symptoms in a case of heart failure, one should consider as possible factors not only drugs, congestion of the abdominal viscera, and disorders of the blood metabolites (such as occur in uremia), but should also entertain the possibility that progressive myocardial disease may be the cause of the symptoms.

2. The mechanism of the nausea and vomiting induced by progressive myocardial disease is believed to be analogous to that caused by digitalis, which has been shown to be due to a reflex arising in the heart itself.

3. When coronary thrombosis occurs in a patient with pre-existing narrowing of the smaller coronary arterial branches, a vicious cycle may ensue; the decline in cardiac output and small pulse pressure lead to further coronary insufficiency and progressive myocardial fibrosis, which bring about a further decrease in cardiac output and perpetuation of the cycle.

4. In cases of heart failure in which there is a small pulse pressure with a high diastolic pressure, the outlook is poor because of the factors outlined.

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Of the twelve patients with symptoms of congestive failure, two were working and ten were not. From this it appears that congestive failure after myocardial infarction is a more disabling complication than angina pectoris.

Of the thirteen patients with mild degrees of both angina pectoris and congestive failure, seven were working and six were not.

Thus, in summary, twenty persons with angina pectoris, congestive failure, or both in mild degree continued to work after recovery from myocardial infarction. It would appear that these sequelae, when sufficiently mild, are compatible with continued employment. The two patients with auriculoventricular heart block and cerebral thrombosis did not return to work.

TABLE III. INDUSTRIAL STATUS OF THIRTY WORKING SURVIVORS (43 PER CENT OF TOTAL SURVIVORS)

	NUMBER OF PATIENTS	PERCENTAGE OF TOTAL SURVIVORS
Working at same job	19	27
Manual labor	15	
Sedentary work	4	
Working at different job	11	16
Lighter physical work	6	
Sedentary work	5	

Table III summarizes the industrial status of the thirty survivors who were working at the end of the survey period. This group constitutes 35.7 per cent of the total number of patients and 43 per cent of the survivors. Nineteen of these patients returned to the same job which they held prior to myocardial infarction. Eleven returned to a different, lighter job. Thus, 27 per cent of the survivors were working at the same job they had previously held at the end of the survey period, and 16 per cent were working at a lighter job. Of those who returned to their old jobs, fifteen returned to manual labor and four returned to sedentary work. Of those who returned to lighter work, six returned to lighter physical work and five accepted sedentary positions. Table I should be compared at this point with Table III.

Of the sixty-five patients whom we studied who were doing manual labor, fifteen, or almost one-fourth, returned to manual labor. Of the nineteen patients who were doing sedentary work, only four, or about one-fifth, returned to it. Omitting altogether those persons who returned to lighter work, which would tend to weight the balance even more in favor of those previously doing manual labor, it is our observation in this relatively small series of cases that persons doing manual labor have at least as good a chance of returning to their old jobs, and certainly as good a chance of returning to some remunerative occupation after recovery from myocardial infarction, as do those persons doing sedentary work.

Table IV summarizes the industrial history of the fifty-four patients who were not working at the end of the survey period. This includes the fourteen who were dead and the forty living but not employed.

Eight patients died within four weeks after the first myocardial infarction, a mortality rate of 9.5 per cent. This figure is not significant because it obviously does not indicate the mortality rate of coronary occlusion with myocardial infarction. The only cases included in our study were those in which the patient survived long enough to have an electrocardiogram taken, or those in which the patient had myocardial infarction at some time which was not immediately recognized or diagnosed, and was recognized later by electrocardiographic study and a recheck of the history.

TABLE I. TYPE OF WORK OF ALL PATIENTS BEFORE MYOCARDIAL INFARCTION

Manual labor	65 patients (75%)
Light or sedentary work	19 patients (25%)

The average period of observation after the occurrence of myocardial infarction was 11.7 months.

The incidence as to sex, race, and age was not remarkable.

The occupational classification was most interesting (Table I). Sixty-five patients, constituting 75 per cent of the series, performed manual labor. Only nineteen patients, or 25 per cent, could be classified as performing other than manual labor. This is particularly significant because other studies[4, 5] have been made on groups which were constituted mainly of "white collar," business, and professional people.

Follow-up study included both clinical observation and employment history.

RESULTS

Medical.—Fourteen of the eighty-four patients died during the period of study. Nine of these died immediately (within four weeks of infarction), which is an immediate mortality rate of 9 per cent for the ninety-seven infarctions.

Table II summarizes the medical status of the seventy surviving patients. Only twenty patients, a little more than one-fourth of the survivors, made a complete symptomatic recovery. Twenty-three patients, a third of the survivors, had subsequent angina pectoris. Twelve patients had congestive failure. Thirteen patients had mild degrees of angina pectoris, as well as congestive failure. There was one case of complete auriculoventricular block and one of cerebral thrombosis.

TABLE II. PRESENT STATUS OF SEVENTY SURVIVING PATIENTS

MEDICAL STATUS	WORKING	NOT WORKING	NUMBER OF CASES	PERCENTAGE OF TOTAL
Complete symptomatic recovery	10	10	20	28.6
Angina pectoris	11	12	23	32.8
Congestive failure	2	10	12	17.1
Angina pectoris and congestive failure (mild)	7	6	13	18.6
Complete A-V block	0	1	1	1.45
Cerebral thrombosis	0	1	1	1.45
Total	30	40	70	100.0

Employment.—With regard to the employment status of the seventy patients surviving at the conclusion of the study (April 20, 1944), Table II indicates that twenty were working and forty were not.

Of those patients who made a complete symptomatic recovery, ten were working and ten were not. Of the ten persons in this category who were not working, nine were unemployed because of personal reasons or some unrelated illness. Of the ten who continued at work, three went to lighter work, but seven returned to the same job they were doing before myocardial infarction.

Of the twenty-three patients who suffered from some degree of angina pectoris alone, eleven were working and twelve were not at the end of the period of observation. This is superficially comparable to what occurred among those who made a complete symptomatic recovery, but in this group those who were not employed were not working because of the angina pectoris from which they suffered.

more than one year. Of the eleven patients in our series who had two myocardial infarctions, four returned to work after the second coronary occlusion. One worked eight months, and was still working at the end of the survey. Two others had worked a few months and were still employed, and one had had to stop after almost a year.

Of particular interest is the fact that ten patients worked through the critical period after coronary occlusion; they took less than one week off for the acute illness, which, for one reason or another, was not promptly diagnosed. Most of these did not consult a physician at all. The observation that some people are able to continue their normal activity, even though it is strenuous, in spite of the occurrence of acute myocardial infarction is not new. It is to be expected that, if the area of myocardium affected by the infarction is small enough, cardiac function will not be seriously impaired, and normal activity can be continued in spite of mild or even moderate discomfort. Recovery may be expected in some, if not in all, such cases. The occurrence of painless myocardial infarction is recognized, and French and Dock[9] report the case of a young soldier who was able to carry on the duties of an active military life without apparent distress in spite of extensive myocardial infarction with mural thrombus formation.

COMMENT

The relation of coronary occlusion to effort or industry is subject to some disagreement, particularly legal. Medical opinion, as expressed by Willius[10] and Master and Dack,[5] is that there is no causal relationship. Master and Dack,[5] after reviewing the histories of four hundred fifteen patients who survived acute coronary occlusion with myocardial infarction, concluded that the incidence of heart failure, subsequent infarction, or subsequent death was not any greater among those who returned to work than among those who did not.

In our series of patients it is to be expected that several who have not yet returned to work will do so in the future. Naturally, some who are working now will drop out, but, as those presently employed continue to work, the average duration of employment after myocardial infarction can be expected to rise.

It is certainly not to be expected that every employed person who suffers acute coronary occlusion with myocardial infarction, and survives, will recover sufficiently to return to work, but it is apparent that many do recover to such a degree that return to full activity may be permitted without the occurrence of any symptoms or fear of shortening life or precipitating a second coronary occlusion. Master, Dack, and Jaffe[11] report that, in a series of two hundred two patients who were followed for two to eight years, 33 per cent made a good recovery, and 50 per cent returned to work, usually at full time.

After ample time has been allowed for full recovery and the formation of a firm scar, those patients who are symptomatically well enough should be permitted to resume employment under adequate medical supervision. The work they are permitted to do should be limited only by their cardiac reserve, or, in other words, their ability to perform their tasks without untoward symptoms. Arbitrary standards governing the type of work permitted for persons who have had myocardial infarction cannot be set up, but in those industries in which medical supervision of certain groups of patients is available, the physician can, with the cooperation of the employer, return many such persons to productive labor.

TABLE IV. INDUSTRIAL HISTORY OF FIFTY-FOUR NONWORKING PATIENTS (64.3 PER CENT OF TOTAL PATIENTS)

		NUMBER OF PATIENTS	PERCENTAGE OF TOTAL PATIENTS	AVERAGE TIME WORKED AFTER FIRST OCCLUSION	
Died within four weeks of first myocardial infarction		8	9.5		
Returned to work, but did not continue work, because of		26	31.0		
A. Chronic cardiac disability	15			10 Months	
B. Second myocardial infarction	5 (2 deaths)			22 Months	13 Months
C. Sudden death without coronary occlusion	1			11 Months	
D. Nonmedical reasons	5				
Failed to return to work because of		20	23.8		
A. Chronic cardiac disability	14				
B. Unrelated fracture	1				
C. Death more than four weeks after infarction	3				
D. Advice of physician	1				
E. Nonmedical reasons	1				

Twenty-six patients returned to work, but did not continue. The reasons are listed in Table IV. The great majority of these were unable to continue at work because of some cardiac disability. In three instances death terminated the work period. In eighteen, symptoms of heart disease were responsible for stopping work. Only five of these failed to continue because of nonmedical reasons. Of the twenty-one patients who returned to work, but were unable to continue because of cardiac disability of some sort, the average period of employment was thirteen months. The work period was longest among those who were forced to discontinue work by the occurrence of a second myocardial infarction, but, since this group is quite small, no conclusions can be drawn.

Twenty patients who survived more than four weeks failed to resume work after coronary occlusion with myocardial infarction. The majority of these (fourteen) continued to have disabling cardiac symptoms. The deaths of three patients occurred late, i.e., more than four weeks after the occurrence of acute myocardial infarction. One patient recovered from the symptoms of cardiac insufficiency, but was unable to return because of a fractured ankle, with complications. One patient failed to return to work because of nonmedical, personal reasons, and in only one case was a patient who recovered from symptoms of cardiac disability advised by a physician not to resume work. As a result of this advice, the patient did not request re-employment.

Analysis of the group of twenty patients who remained unemployed justifies the inference that, in this series of patients, a desire to return to work or the necessity of doing so was almost universal. Nineteen of the twenty persons who did not resume work after their first coronary occlusion failed to do so because of medical reasons, and in only one instance was a nonmedical, personal reason responsible for failure to return to some sort of work. Speculation as to whether so many would have tried to work if their income were otherwise assured is warranted, but the fact that these persons were almost forced to try to earn a living makes observations regarding their ability to do so more reliable.

Of the entire group of fifty-six patients who returned to work after their first myocardial infarction, eighteen, or 32 per cent, were able to continue

without discomfort, with the restriction that such a person should not be permitted to take a job in which his sudden collapse might endanger his safety or the safety of others.

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THE RELATION OF RESTING HEART RATE TO THE INCREASE IN RATE DUE TO EXERCISE

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IT HAS been frequently assumed that there is a high positive correlation between resting heart rate and increase in rate due to exercise. During the course of experiments dealing with the reliability and validity of cardiovascular measures, it was observed that, as a rule, there was little or no relationship between resting heart rate and increase due to exercise.

Although no published reports were found in which resting heart rate was correlated with increase in rate due to exercise, data were found which were suitable for investigating this point. Jokl, et al.,[1] studied numerous physiologic responses of thirty-two South African recruits over a twenty-four-week physical training period. Their data included resting heart rates and postexercise heart rates obtained before the program began and at six-week intervals throughout the training period. The exercise which Jokl employed was forty knee bends performed in one minute. These data were adapted to our purpose by subtracting the resting heart rate from the postexercise count. Coefficients of correlation were calculated for resting heart rate and increase in rate due to the exercise for each interval at which data were secured. Five correlations were obtained: Beginning, −0.411; six weeks, −0.185; twelve weeks, −0.394; eighteen weeks, −0.377; twenty-four weeks, −0.484. In each instance it is seen that the correlation between resting heart rate and increase in rate due to exercise is negative.

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Received for publication Aug. 8, 1944.

It is the responsibility of the physician who is guiding the convalescence of his patient to return him, if possible, to productive work. Since it is difficult to train many people, particularly those who are doing manual labor, for an entirely different type of work, and since the number of sedentary jobs available is limited, considerable encouragement can be derived from the observation that many persons are able to return even to manual labor. Optimism regarding the work prognosis of such persons is warranted when it is seen that symptomatic recovery and an approach to normal functional capacity are proceeding satisfactorily.

The possibility of the occurrence of sudden death among persons who have angina pectoris or arteriosclerotic heart disease indicates some restriction as to the type of jobs these employees may be assigned. It would be unwise and unsafe to allow such a person to hold a position in which sudden failure of one man might endanger the life or safety of others. It would also appear unwise to permit such a person to engage in an occupation in which sudden collapse or pain might result in harm to him, either by a fall or by loss of control of machinery.

SUMMARY

Eighty-four patients who had ninety-seven myocardial infarctions before Jan. 1, 1944, were studied, of whom 75 per cent were manual laborers. The period of study ended April 20, 1944.

The average period of observation was 11.7 months.

Fifty-six patients (66.6 per cent of the total, and 73.7 per cent of those surviving four weeks) returned to work after myocardial infarction.

Thirty patients (43 per cent of the survivors and 35 per cent of all observed) returned to work and were still working at the conclusion of the period of study.

Of these, nineteen returned to the same type of work they were doing before infarction occurred.

Eleven of them returned to lighter work.

Neither angina pectoris nor slight congestive failure nor mild degrees of both prevented twenty patients from returning to gainful employment.

Only twenty (23.8 per cent) of our patients made a complete symptomatic recovery.

The probability that manual laborers may be able to resume their former employment after myocardial infarction appears to be no less than for sedentary workers.

Twenty-six patients (31 per cent of all observed) returned to gainful employment, but did not continue. Of the twenty-one who were disabled by arteriosclerotic heart disease, the average time worked after myocardial infarction was thirteen months.

Twenty patients who survived the initial critical period failed to return to work, eighteen because of heart disease.

Eighteen patients (32 per cent of those returning to work) were able to work more than one year after recovery from acute myocardial infarction.

CONCLUSIONS

The diagnosis of coronary occlusion with myocardial infarction should not of itself disqualify a man for employment or re-employment, even in a heavy industry or at manual labor. Subsequent employment should depend upon the cardiac reserve after recovery, or the ability of the patient to perform his work

TABLE I. THE EFFECT OF THE STRENUOUSNESS OF EXERCISE ON THE CORRELATION OF RESTING HEART RATE WITH INCREASE IN RATE DUE TO EXERCISE

SUBJECTS	EXERCISE	COEFFICIENT OF CORRELATION BETWEEN RESTING RATE AND INCREASE DUE TO EXERCISE
20 men	60 rev./min.	0.281
18 men	maximum /2 min.	-0.731
40 women	40 rev./min.	0.012
40 women	60 rev./min.	-0.258
31 women	maximum /2 min.	-0.460

sult in a positive coefficient. This idea was tested by having a group of forty women ride the bicycle ergometer at a rate of only forty revolutions per minute for one minute. In this experiment the coefficient of correlation between resting heart rate and the increase caused by the exercise was found to be 0.012, as compare to -0.258 for moderate exercise and -0.460 for strenuous exercise. These data further support the idea that the size and sign of the correlation between resting heart rate and increase in rate caused by exercise depend on the strenuousness of the exercise.

In seeking an explanation for the variability in the sign and size of the correlation between resting heart rate and increase in rate due to exercise, the way by which the resulting increase in minute volume is brought about must be considered. Strenuous exercise is a relative term, and from the standpoint of the individual, what is strenuous depends on his capacity to do work. It is generally recognized that, as capacity to do work increases through physical training, the resting pulse rate is reduced and the stroke volume is increased.[2]

Since this is true, the person in good condition, with a lower resting heart rate than those in poorer condition, will experience less increase in heart rate when he performs a moderate amount of exercise because he makes greater use of increased stroke volume in adjusting to the exercise. Thus, the results obtained from groups of persons of varying degrees of physical fitness doing moderate exercise show a positive correlation between resting heart rate and increase in rate due to exercise.

In order to explain the negative correlation between the resting heart rate and increase due to strenuous exercise, let us assume that the exercise is sufficiently strenuous to cause the heart to reach its maximum rate, which is approximately the same for everyone. The result is that the person with the lowest heart rate has the greatest increase, and the one with the highest resting rate will experience the least increase in rate because of the work. Under these conditions there is a negative correlation between resting heart rate and increase due to exercise.

Evidently, the correlations presented in Table I can be explained by the degree of strenuousness of the exercise which the various subjects performed. The men involved in the experiments were heterogeneous with regard to capacity to do work. For the majority, sixty pedal revolutions per minute for one minute was evidently quite moderate, but for others this work was more strenuous. The result was a small positive correlation between resting heart rate and increase in rate due to the exercise for reasons mentioned. When the men performed maximum work for a period of two minutes, the work was unquestionably strenuous for all, and the result was a high negative correlation. Forty pedal revolutions per minute for one minute proved to be quite moderate for the majority of the women, but more strenuous for some of them, depending on their capacity to do work. The result was a low positive correlation. Sixty pedal revolutions in a minute was evidently quite strenuous for the majority of

Also, data collected from five hundred forty-four college men relative to the response of the heart to exercise were available in our laboratory. The exercise employed was forty stool-steps per minute for one minute. The postexercise heart rate had been obtained by counting the number of beats for a period of two minutes immediately after the exercise. The increase in rate due to exercise was found by subtracting twice the resting rate from the postexercise count. In the case of this group of men, the coefficient of correlation for resting heart rate and increase due to exercise was found to be 0.203.

In order to obtain additional information concerning the relation of resting heart rate to increase in rate caused by exercise, data were collected from twenty college men and forty college women. To increase the reliability of the values obtained from each person, each subject came to the laboratory four times, at weekly intervals. Each time, after the resting heart rate was established for the subject in a recumbent position, he or she rode a bicycle ergometer at the rate of sixty revolutions per minute for one minute. The work performed was 1,500 kilogram-meters. As soon as the work was completed the subject resumed the reclining position. The increase in heart rate due to the exercise was found by subtracting the resting rate from the postexercise rate. The mean values for the four experiments were used in establishing the resting rate and the increase due to exercise. When these values were correlated, a coefficient of 0.281 was obtained for the men; for the women the coefficient was –0.258.

As shown by all of these experiments, there is obviously a variable relationship between resting heart rate and increase in rate due to exercise. It is of interest that, in the case of the college men, the correlation is positive, whereas, for women doing exactly the same kind and amount of exercise, it is negative. It occurred to us that the explanation of this situation might be that the relation existing between resting heart rate and the increase caused by exercise is influenced by the strenuousness of the exercise. It might be supposed that sixty revolutions of the bicycle per minute for one minute was relatively strenuous for the women, with the result that there was a negative correlation between resting heart rate and the increase caused by the exercise. In the case of the men, it might be that the positive correlation was associated with the fact that sixty pedal revolutions on the bicycle for one minute constituted comparatively moderate exercise.

In order to gain further information relative to the effect of the strenuousness of exercise on the nature of the response of the heart to exercise, additional experiments were carried out. Eighteen of the twenty college men and thirty-one of the forty college women used in the previous experiment were available. They were asked to perform exercise which was unquestionably strenuous. After a resting heart rate was established, each subject rode the bicycle ergometer at top speed for two minutes. Immediately after the exercise the increase in heart rate caused by the work was calculated as in the previous experiment. In the case of the men, the coefficient of correlation between resting heart rate and increase in rate caused by the exercise was found to be –0.731, as compared to 0.281 for the milder exercise (Table I). For the women in this experiment the coefficient was –0.460, as compared to –0.258 for the less strenuous exercise. These results confirm the belief that the more strenuous exercise is, the more negative the coefficient of correlation between resting heart rate and increase due to the exercise becomes.

It is reasonable to suppose that, if the more strenuous exercise causes the correlation described above to become more negative, light exercise should re-

furnished not only valuable statistical information, but also unexpected viewpoints.[1] Among these has been the realization that bacterial endocarditis of both the acute and subacute varieties is far less rare in old persons than we had heretofore realized. We have collected from the clinical records of the Medical Services and from the protocols of the Pathologic Laboratory, covering ten years, the following groups: acute bacterial endocarditis, nine cases in patients ranging from 60 to 80 years of age; and subacute bacterial endocarditis, eighteen cases in patients ranging from 60 to 87 years of age. The age of 60 has been taken as a minimum, partly as an arbitrary, convenient point of reference and partly because by that time all persons show definite evidence of aging, although this process begins earlier in life and often is well developed before this period. The present contribution will be limited to a consideration of the cases of acute bacterial endocarditis.[2]

LITERATURE

In 1843, Graves[3] reported the occurrence in a 66-year-old man of acute endocarditis involving a bicuspid pulmonary valve. The observations of Winge[4] and Heiberg[5] established the bacterial nature of the condition, which was further clarified by Osler's "Goulstonian Lectures."[6] Lenhartz,[7] in his famous work on sepsis, published in 1903, discussed the age incidence of "septic endocarditis"; he pointed out that persons of all ages participate, and that the period of greatest frequency is between 20 and 50 years of age, but he had seen three cases in persons between 10 and 20 years, and on the other hand, four cases in persons from 60 to 70 years of age.

Thayer's classic study[8] contains a valuable statistical analysis of the age incidence of the various forms of bacterial endocarditis. "A considerable majority of the gonorrheal series occurred in individuals between 20 and 30, which corresponds, probably, fairly well to the period of greatest promiscuous sexual activity. The curve in our small influenzal series reaches its peak in the third decade. One-half the patients were under 30; one-half between 30 and 60. Influenzal endocarditis prevailed in early and middle adult life. Streptococcal endocarditis, while occurring at all ages prevailed in middle adult life. The curve for viridans endocarditis reached its peak in the third decade, that for acute streptococcal endocarditis in the fourth. The age curve of pneumococcal disease of the heart, on the other hand, is different. The rise begins in the third, reaching its peak in the fifth decade. Over 60 per cent of the patients in the pneumococcal series were over 40 years of age; 32 per cent over 50. Pneumococcal endocarditis was a disease of middle and later adult life. Staphylococcal (aureus) infections, while prevailing under the age of forty, were met with more or less indifferently throughout life."

White,[9] in his textbook, makes the broad generalization: "Acute bacterial endocarditis may occur at any age from infancy to old age." Herrmann[10] is more explicit: "Secondary type of acute bacterial endocarditis, commonly encountered in the presence of definite septic focus . . . may occur in any age group, more commonly in adults and middle-aged persons and less often in the aged and infants."

Several recent reports on acute bacterial endocarditis bear on the question of age incidence. In Ruegsegger's[11] report on pneumococcus endocarditis, four cases in patients over 60 years old are included. He points out that, whereas 50 per cent of all of his patients with pneumococcus infections were below the age of 40 years, 80 per cent of the endocarditis group were beyond this limit.

the women, and the result was a low negative correlation. When the women worked at maximum power for two minutes, the exercise was very strenuous and the result was a higher negative correlation.

CONCLUSIONS

The size and sign of the coefficient of correlation between resting heart rate and increase in rate due to exercise depend on the strenuousness of the exercise.

A group of persons whose physical condition varies from poor to good, doing mild or moderate exercise, will give either a small negative or a small positive correlation, depending on which type predominates. If the majority of them are in good physical condition, the result will be a small positive coefficient of correlation. If the converse is true the result will be a small negative coefficient.

Strenuous exercise results in a high negative correlation between resting heart rate and increase in rate caused by exercise. This is due to the fact that every person in the group approaches the maximum rate, so that those with the lowest resting rate experience the greatest increase, whereas those with higher rates experience less increase.

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ACUTE BACTERIAL ENDOCARDITIS IN THE AGED

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INTRODUCTION

THE increasing number of men and women who attain advanced age has produced a complex series of social, economic, and medical problems. The necessary awareness of physicians is reflected in the growing list of publications on the medical aspects of old age. It is becoming apparent to the practitioner that, with the decrease in the incidence of acute infections among young people, together with improved therapeutic methods, an ever growing proportion of his patients will have passed the ages of 50 and 60 years. This situation calls for careful clinical evaluation of disease pictures in the aged in terms of present-day medicine. The study of senescence, as well as the diagnosis and treatment of disease in the aged, is a natural function of the internist. The word "geriatrics," coined in 1914, by Nascher, "to cover a special branch of medicine dealing with old age," is of great utility as a comprehensive term, but its employment should in no way obligate us to segregate a new medical specialty.

For some time the analysis and study of a large number of post-mortem examinations on persons over 60 years of age have occupied us, and have

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Received for publication Aug. 11, 1944.

the base of the left lung. The heart sounds were of fair quality; a harsh systolic murmur was heard all over the precordium. The peripheral vessels were moderately sclerotic. The abdomen showed well-healed right upper and left upper quadrant scars. The liver was palpable. The blood pressure was 140/80. The hemoglobin was 89 per cent, and the leucocyte count, 13,600, of which 88 per cent were polymorphonuclears. The urine showed a trace of albumin, 10 per cent sugar, heavy traces of acetone, and occasional hyaline casts and erythrocytes. Spinal puncture revealed a purulent fluid containing numerous gram-positive organisms, mostly diplococci. In view of the fact that meningococci occasionally may be gram-positive at first, antimeningococcus serum was administered intraspinously and intravenously. A consultant for nose and throat diseases found no evidence of suppuration in the sphenoid and ethmoid sinuses. A pneumococcus, Type XXVIII, was recovered from the spinal fluid, from the blood, and from the secretion of the right sphenoid. For this reason, exploratory bilateral sphenoethmoidectomy was performed, but no frank suppurative focus was encountered. After the operation the temperature rose sharply to 106.8° F., and patient died twenty-four hours later. The glycosuria and acidosis had been controlled by insulin.

Post-mortem examination revealed the following: acute, purulent menignitis (pneumococcus, Type XXVIII); acute pneumococcus, Type XXVIII, endocarditis of mitral and aortic valves; chronic rheumatic heart disease, mitral valve; coronary sclerosis without narrowing; a patent foramen ovale; nephrocirrhosis atherosclerotica lenta incipiens; fibroadenoma of the prostate; a colloid adenoma of the thyroid; and the status six years after cholecystectomy and one and one-half years after splenectomy.

Comment.—The portal of entry here was the accessory nasal sinuses, infection of which led to blood stream invasion, with subsequent acute endocarditis and suppurative meningitis. Noteworthy was the involvement of both mitral and aortic valves, although the pathologist found evidence of old rheumatic valvular lesions only on the mitral leaflets. The spleen, removed a year and a half before, had shown microscopic changes which were interpreted as being due to chronic infection, but there is no reason to believe that there was any connection between the antecedent splenic disease and the fatal illness.

CASE 2.—*Pneumococcus, Type III, ear infection in a 63-year-old woman with diabetes; acute mastoiditis; simple mastoidectomy and obliteration of lateral sinus because of purulent thrombosis. Twenty-four days later, chills and fever; blood culture positive for pneumococcus, Type III; reoperation and dural vein exploration; extension into opposite sinus found. At autopsy, bilateral lateral sinus thrombophlebitis, and acute pneumococcus, Type III, endocarditis of aortic valve.*

This patient, known to have diabetes, was admitted to the Mt. Sinai Hospital April 20, 1937, because of aural pain and discharge from the ear for one week, following an upper respiratory infection. At this time the diabetes was not under control. Culture of the discharge disclosed a pneumococcus, Type III, and roentgenologic examination showed mastoid involvement. Mastoidectomy revealed the extensive bony destruction which is characteristic of pneumococcus, Type III, infection. Creamy, thick pus appeared when the lateral sinus was incised. There was no bleeding from the bulbar end, and only a moderate amount from the torcular end. The patient did very well, and was out of bed walking about, when, on the twenty-fourth day after the sinus operation, she suffered a chill, and fever again set in. A blood culture disclosed pneumococcus, Type III. The patient was immediately operated on again; the internal jugular vein was ligated, and the dural sinuses were re-explored. There was evidence of extension into the straight sinus and into the opposite side. The patient died June 23, 1937.

Post-mortem examination revealed the following: bilateral lateral sinus thrombophlebitis; acute pneumococcus, Type III, endocarditis, aortic valve; chronic rheumatic disease, mitral and aortic valves; coronary sclerosis, without narrowing; pulmonary emphysema; generalized arteriosclerosis; and obesity.

Comment.—This patient illustrated the characteristic course of pneumococcus, Type III, infections of the mastoid, which have so long baffled the otologists. Here, too, the endocarditis was clearly secondary to blood stream infection following mastoid and lateral sinus infection. Old rheumatic valvular lesions were present. The administration of sulfanilamide at time of the first

Moragues and Anderson[12] report a case of acute endocarditis due to *Pseudomonas aeruginosa (Bacillus pyocyaneus)*. The patient, a 66-year-old man, was admitted because of urinary tract infection by this organism. Repeated blood cultures showed *P. aeruginosa*, and the patient succumbed with terminal signs of acute meningitis. Although examination of the heart had been negative during life, necropsy revealed an old mitral stenosis, with a superimposed acute endocarditis. These authors list five additional cases of endocarditis due to the same organism. Of these, one[13] occurred in a man, 65 years old, following contaminated intravenous injections, and another,[14] in a man, 71 years old, was secondary to urinary tract infection.

In a Cabot case report[15] on pneumococcus endocarditis in a man, aged 64 years, meningitis again appears to have been a terminal manifestation. In a 75-year-old man suffering from acute bacterial endocarditis due to an unidentified organism, Bartol, Edwards, and Lamb[16] found a dissecting aneurysm of the aorta which arose in the base of a complicating mycotic aneurysm.

Other pertinent case reports will be discussed in the section on therapy.

TABLE I. ACUTE BACTERIAL ENDOCARDITIS IN THE AGED

CASE	AGE (YR.)	SEX	ORGANISM (BLOOD CULTURE UNLESS STATED OTHERWISE)	CLINICAL DIAGNOSIS	DURATION OF ILLNESS	PORTAL OF ENTRY	COMMENT
1	61	M	Pneumococcus, Type XXVIII (also from right sphenoid and spinal fluid)	Pneumococcus meningitis and sinusitis; diabetes	13 days	Nasal sinuses	Died 2 hours after ethmoidectomy
2	63	F	Pneumococcus, Type III	Acute mastoiditis; lateral sinus thrombosis; diabetes	70 days	Ear	Chill, fever 24 days after mastoid operation; treated with sulfanilamide
3	80	F	Pneumococcus, Type VI	Pneumonia	14 days	Lung. Carcinoma of stomach	Unsuspected carcinoma of stomach at autopsy
4	74	F	Pneumococcus, Type XI and *Streptococcus hemolyticus*	Agranulocytosis; necrosis of tonsils	17 days	Tonsils	Onset gradual 2 weeks before admission; no medication
5	62	F	*Streptococcus hemolyticus*	Diabetes; acidosis; cerebral lesion; coronary thrombosis	6 days	Not known	Stuporous on admission; kidneys showed intercapillary glomerulosclerosis
6	70	F	Anaerobic streptococci	Adenocarcinoma of uterus; pyometra	3 weeks	Pyometra	Chills and fever began 3 weeks before death
7	60	F	Enterococcus and *Staphylococcus albus*	Left ureteral calculus; pyonephrosis	18 days	Pyonephrosis	Death 4 days postoperatively
8	65	M	*Staphylococcus aureus*	Bronchopneumonia? Old coronary occl.	3 days	Infection in right toe	Sputum showed pneumococcus, Type VII
9	80	M	*Escherichia coli* from heart valve (smear from vegetation-cocci)	Bronchopneumonia	5 days	Not known	Areas of tender swelling, both external malleoli

CASE REPORTS

CASE 1.—*Pneumococcus Type XXVIII, sinusitis, and meningitis in diabetic man, aged 61 years, who died two hours after bilateral sphenoethmoidectomy. Autopsy showed acute purulent meningitis, and acute pneumococcus (Type XXVIII) endocarditis of aortic and mitral valves.*

The patient was admitted to the Mt. Sinai Hospital March 2, 1937. Eighteen months previously he had undergone splenectomy for splenomegaly and secondary anemia. Five days before admission he suffered a shaking chill, lasting one hour, and followed by a fever of 104° F. He complained of sharp pains shooting up and down his spine, pain in the lower extremities, and severe headache associated with emesis. On examination he appeared acutely ill and was delirious. The pharynx was dry, granular, and injected. Râles were heard at

A blood culture taken at that time was reported thirty-six hours later to contain *Staphylococcus aureus.* The following day an area of redness was noted on the lateral aspect of the right big toe, and two lymphangitic streaks appeared on the dorsal aspect of the foot. There were no petechiae and no evidence of superficial thrombophlebitis. The right dorsalis pedis pulsation, noted as present on admission, became imperceptible. On the day of death, three days after the onset, a bluish, tender discoloration on the palmar aspect of the left hand developed at the base of the metacarpal bones.

Post-mortem examination revealed: acute *Staphylococcus aureus* endocarditis, mitral valve; subacute, incomplete closure of the right coronary artery due to hemorrhage in a plaque; extensive arteriosclerotic narrowing of left circumflex and left anterior descending coronary arteries; acute myomalacia of the posterior wall of the left ventricle; arteriosclerosis of the aorta; acute infarction of the right kidney; and multiple excretion abscesses in both kidneys.

Comment.—A true primary, or cryptogenic, endocarditis was present in this case. The sputum culture would seem to indicate that bronchopneumonia, possibly secondary to congestive heart failure, was due to pneumococcus, Type VII. The blood culture, containing *Staphylococcus aureus,* came as a distinct surprise. The endocardial implant occurred on an otherwise normal valve. A similar case was reported recently in which a 35-year-old woman had suffered from a pneumococcus, Type I, pneumonia and empyema, and at autopsy was found to have a *Staphylococcus aureus* bacteremia and acute staphylococcus endocarditis of the mitral and pulmonary valves.[19]

CASE 9.—*Man, aged 80 years, had gradual onset of pain in right external malleolus and fever for three days; he was moribund on admission, and no diagnosis was made. Autopsy: acute bacterial endocarditis, mitral valve, organism unknown.*

After prostatectomy two years before, this 80-year-old man had occasional hematuria, but was otherwise well until two weeks before admission to the Mt. Sinai Hospital, when he had an attack of so-called indigestion and was in bed for three days. One week before admission he developed pain in the region of the right external malleolus, with pain on motion and redness; two days later there were cough and fever. The patient was in extremis. He was restless and uncooperative, with a clouded sensorium; the pharynx was red and swollen; the chest was barrel shaped, and there were dullness and diminished voice and breath sounds over the lower half of both lower lobes, with numerous medium and coarse moist râles. The cardiac outlines could not be ascertained; the sounds were of very poor quality. Peripheral arteriosclerosis was marked. The blood pressure was 154/82. Abdominal distention interfered with palpation of the viscera. An area of erythema over both external malleoli was observed. He died twelve hours after admission.

Post-mortem examination revealed acute bacterial endocarditis, mitral valve; acute and chronic bronchitis, pulmonary emphysema, bronchopneumonia of left upper and left lower lobes; general arteriosclerosis; and multiple petechiae in the kidneys and ureters. Culture of the vegetation yielded pure *Escherichia coli,* although, on direct smear, many *gram-negative* rods and gram-positive cocci were seen. The bacteriologic observations therefore permitted no definite interpretation.

Comment.—This case shows how difficult clinical diagnosis can be when the patient is moribund when he is seen for the first time. Autopsy revealed acute endocarditis, but we are entirely in the dark as to its pathogenesis and the causative organism, although the bronchopneumonia must be considered as a possible primary focus.

PATHOLOGY

For a general description of the pathology of acute bacterial endocarditis, the reader is referred to the textbooks of Aschoff, Kaufmann, and MacCallum, and to the monograph of Libman and Friedberg[21] for a comprehensive discussion of the pathologic changes in subacute bacterial endocarditis, with particular emphasis on the differentiation between the two forms. At this point it is our purpose simply to point out certain outstanding pathologic features of our cases.

operation was not effective in clearing up the infection. The action of these drugs in cases of ear disease, in which they often cause temporary improvement and thus promote a false sense of security, has been pointed out by Maybaum, Snyder, and Coleman.[17]

CASE 3.—*Daily shaking chills and pyrexia in a woman, aged 80 years; cause obscure until, on eleventh day of illness, the second blood culture contained a pneumococcus (Type VI). Sulfapyridine therapy caused thrombocytopenic purpura and skin eruption. Died thirteen days after first chill. Post-mortem examination: acute pneumococcus (Type VI) endocarditis, mitral and aortic valves, with perforation of anterior mitral and left aortic cusps.*

The patient was admitted to the Mt. Sinai Hospital Nov. 20, 1940, with the history that seven days before she had noted nausea and emesis without obvious cause, and five days before had had a shaking chill with a temperature rise to 103° F. Thereafter chills occurred daily. Examinatiou revealed obesity, deafness, fever, evidence of right-sided iridectomy for glaucoma, pulmonary emphysema, crackling râles at the bases of both lungs, a high-pitched, rough systolic murmur at both aortic and mitral areas, and a distended abdomen. The hemoglobin was 80 per cent, and the leucocyte count, 8,600, of which 56 per cent were segmented, 25 per cent nonsegmented, 12 per cent lymphocytes, 6 per cent monocytes, and 1 per cent, basophiles. The urine was clear and acid, and contained a trace of albumin and occasional granular and cellular casts. The blood urea nitrogen was 37 mg., and the cholesterol, 210 milligrams. The first blood culture was sterile. The second (Nov. 26, 1940) showed pneumococcus, Type VI. Excretion pyelograms were normal. A roentgenogram of the chest showed numerous miliary and submiliary infiltrations of the lower two-thirds of the right lung, and an irregular area of density in the left lower lobe behiud the heart, probably an area of consolidation. A barium enema showed nothing abnormal. An electrocardiogram revealed no significant change. Sulfapyridine therapy was started on admission, but did not affect the septic temperature curve. On the sixth day after entry an erythematous rash appeared on the trunk and left upper extremity. In addition, a number of purpuric spots were noted in the conjunctivae. The blood platelets had dropped to 50,000. Because of the thrombopenia, the sulfapyridine was discontinued, and the patient was given antipneumococcus, Type VI, rabbit serum. The patient died two days later.

At autopsy the following diagnoses were established: acute pneumococcus (Type VI) endocarditis of mitral and aortic valves, with perforation of anterior mitral and left aortic cusps; acute focal myocarditis at point of contiguity with mitral vegetation; chronic rheumatic heart disease, mitral valve; carcinoma of stomach; large, benign, prepyloric polyp; embolus in superior mesenteric artery; and marked sclerotic narrowing of the ostium of the celiac axis.

Comment.—The portal of entry of the infection in this case could not be established with certainty. Both the lungs and the clinically unsuspected carcinoma of the stomach must be considered. Here we may speak of a primary, or idiopathic, endocarditis in which the signs of blood stream infection far overshadowed the localizing manifestations. The association of the gastric neoplasm with a benign prepyloric polyp is of interest from the standpoint of the metaplasia of benign lesions in the gastrointestinal tract.

CASE 4.—*Cryptogenic agranulocytosis of nineteen days' duration in a woman 74 years old, associated with mixed infection of the blood stream by a pneumococcus, Type XI, and Streptococcus hemolyticus, probably secondary to gangrenous pharyngitis and tonsillitis. Post-mortem examination: bacterial endocarditis of pulmonary, mitral, and aortic valves.*

The patient was admitted to the Mt. Sinai Hospital April 9, 1934. She had been in relatively good health until two weeks before admission, when fever, sore throat, and weakness were noted. No medicine of any kind had been taken. There had been no chills. Physical examination disclosed that the pharynx was red and congested, and the tonsils large, swollen, and covered with easily removable grayish-white membrane, removal of which caused no bleeding. The upper anterior cervical nodes were large and tender. The heart, except for numerous extrasystoles, exhibited no abnormalities. The lungs were hyperresonant; the expiratory phase of respiration was prolonged, and numerous sibilant and sonorous râles were heard. The hemoglobin was 68 per cent, and the leucocyte count, 1,900, with 98 per cent lymphocytes and 2 per cent monocytes.

is unhampered by the added burdens so common in later years. Three of the nine patients, for example, suffered from diabetes mellitus, and two of these had diabetic acidosis on admission to the hospital.

BACTERIOLOGY

Pneumococci of various types were cultured from the blood in four of the nine cases. In one of these a hemolytic streptococcus was also found. By including the enterococcus in the streptococcus group, we find that this species was also recovered in four cases, of which two were the hemolytic variety. *Staphylococcus aureus* occurred in one case, and, in another, *Staphylococcus albus* was associated with the enterococcus. It will be recalled that both Ruegsegger[11] and Thayer[8] emphasized the occurrence of pneumococcus endocarditis in the higher age groups. The latter also pointed out that staphylococcus endocarditis, although it occurs at all ages, was most common in the third and fourth decades.

In connection with the two cases of mixed infection, we call attention to a recent contribution by Orgain and Poston,[18] in which they report six patients with bacterial endocarditis from the blood of whom they repeatedly cultured two or more distinct species of bacteria. There was little in the history, physical and laboratory data, and clinical course of their patients to suggest a mixed infection. They emphasize that recognition of a mixed infection is of fundamental importance in sulfonamide therapy, for the drug may affect one organism and not the other.

The difference in the bacterial content of the blood stream and the sputum is noteworthy in Case 8, in which the sputum yielded pneumococcus, Type VII, and the blood, *Staphylococcus aureus.* A similar situation was recently reported from Boston,[19] and was mentioned in the comment on Case 8. A woman, aged 53 years, died, as it semed, from pneumococcus, Type I, pneumonia, and empyema. Post-mortem examination disclosed, in addition, acute staphylococcus endocarditis and bacteremia.

The portal of entry of the infective agents was clear in five cases of this series, questionable in two, and not known in two. The clear origins of the bacteremia were acute nasal sinusitis, middle ear infection and mastoiditis with sinus phlebitis, agranulocytosis with gangrenous mouth lesions, pyometra, and pyonephrosis. In the dubious cases the bacteremia may have originated either in the lungs or a gastric neoplasm in one instance, and, in the other, in an infection of the great toe, which was more likely a result than a cause of the sepsis. In the remaining two cases (Cases 5 and 9) no portal of entry could be recognized with certainty.

CLINICAL PICTURE

In none of these nine cases was the correct diagnosis made, or even suspected, ante mortem, in spite of the demonstration of bacteremia in several. The continuing fever and progressive downward course of the patient were often ascribed to the obvious presenting condition, as in Case 7, in which the infected adenocarcinoma of the uterus seemed an adequate explanation for the observed symptoms and signs. In Case 5 the clinical manifestations were explained as the result of one of several possible conditions, i.e., diabetic acidosis, coronary thrombosis, or cerebral hemorrhage. In Case 8 the easily detected bronchopneumonia due to pneumococcus, Type VII. seemed an adequate diagnosis until *Staphylococcus aureus* was found in the blood stream. In general, the multiplicity of lesions causing symptoms and physical signs in the aged accounts for

The valvular lesions consisted of the typical, large, friable vegetations in which freshly made smears showed masses of bacteria. The mitral valve was involved in all but one case (Case 2), and in five cases was the only one involved. The aortic valve was involved alone in one case (Case 2), together with the mitral valve in two cases (Cases 1 and 3), and with the mitral and pulmonary valves in one case (Case 4). In Case 3 both the anterior mitral and the left aortic cusps were perforated by the inflammatory process, giving rise to the picture of what the older pathologists termed "ulcerative endocarditis." At the point where the vegetation on the under side of the mitral valve came in contact with the lateral wall of the ventricle there was a localized area of endocardial inflammation, with involvement of the underlying myocardium.

In four out of the nine cases, definite, old rheumatic lesions involving the mitral valve were found. In one of these (Case 2) the aortic valve was similarly involved. In spite of the age of the patients in this series, in only one (Case 8) was there any arteriosclerotic thickening of the valve. In four of the nine cases no previous valvular damage of any kind could be found.

As to the occurrence of embolic phenomena, in three cases (Cases 1, 6, and 7) there were none. In Case 2 there was microscopic evidence of acute myocarditis. In Case 3, embolism of the superior mesenteric artery was found; this had apparently occurred shortly before death. In Case 5 a myocardial abscess was found, and examination of the brain revealed toxic encephalopathy. Kernohan, Woltman, and Barnes,[20] in discussing involvement of the central nervous system in association with endocarditis, have pointed out that "changes in the central nervous system with or without clinical symptoms are not only common to all types of endocarditis, but also are distinctive." Case 8 was the only instance in the series of multiple excretion abscesses of the kidneys. The embolic lesions of the skin will be taken up in connection with the discussion of the clinical picture.

In a group of aged persons, the significance of the associated conditions cannot be overemphasized. By this we do not mean such manifestations as the meningitis in Case 1, the latent sinus phlebitis in Case 2, or the carcinoma of the uterus in Case 6, for these conditions are to be regarded as part of the chain of events definitely leading to sepsis. In four cases (Cases 4, 5, 8, and 9), diffuse gross arteriosclerosis was present. In Case 3, arteriosclerotic narrowing of the ostium of the celiac axis was found, in addition to an undiagnosed malignant neoplasm of the stomach and a benign polyp of the stomach. In Case 5, the kidneys were the seat of the lesion now known as intercapillary glomerulosclerosis; in addition, there were marked narrowing of the coronary arteries and myocardial fibrosis. In Case 8, myocardial infarction due to coronary thrombosis occurred six months previously, with consequent functional impairment. In Case 9, both acute and chronic bronchitis were found. To what extent these conditions, especially the generalized arteriosclerosis and the arteriosclerosis of the coronary vessels, influenced the clinical picture cannot be stated definitely, but it may be fairly assumed that these abnormalities do reduce the functional capacity of the tissues and the organs, and of the body as a whole. We believe that it is changes such as these that make the clinical picture of disease in the aged different from that in the young, for in the latter group the tissues and organs are unaltered either by associated diseases or the processes of senescence. In other words, if a disease picture is the result of the interaction of a pathogenic organism and the defense mechanisms of the human body, the variables are the virulence of the organism and the reactive power of the body, which in youth

is obvious that, when the possibility of endocarditis is unsuspected, little time will be given to looking for skin lesions.

It may be urged by some that acute bacterial endocarditis in the aged is a "terminal" or "agonal" manifestation. We believe rather that it may be at times a "terminating" condition, since no one can deny that, in some of these cases, there was the possibility of prolongation of life had not this condition supervened. The development of endocarditis may be the decisive factor in bringing about the fatal issue.

DIFFERENTIAL DIAGNOSIS

It is clear from the foregoing that acute bacterial endocarditis may complicate any infectious disease in old people. It is to be considered as a diagnostic possibility in any febrile condition in the aged which is associated with bacteremia, and the more so if there is no response to specific therapy.

The differentiation from subacute bacterial endocarditis is important because, in our experience with the aged, the latter variety is twice as common as the acute, and, although it presents great diagnostic difficulties in old people, may more often be correctly diagnosed, because these patients are under observation for longer periods of time. Libman and Friedberg[21] have emphasized that, whereas in the acute form the primary lesion may overshadow the endocarditis, in the subacute type "the symptoms are due to the endocardial involvement or its complications. . . . The endocardial lesions produce symptoms by way of the associated toxemia and bacteremia, because of their effect on the valves and adjacent structures, and because the release of particles from the vegetations, usually containing bacteria, produces embolism and embolic aneurysms." As our series shows clearly, the course of the acute type is fulminating, and often diagnostically obscure by reason of the prostration of the patient, which tends to mask the symptoms. Commonly, the wealth of symptoms and signs makes it difficult to explain the clinical manifestations as a result of one disease. This is, of course, a frequent experience when dealing with aged patients, and has in part given point to the clinical aphorism: Disease in the aged is characterized by multiplicity, chronicity, and duplicity.

THERAPY

Medical opinion, until very recently, agreed that there was no treatment for acute bacterial endocarditis that offered even a moderate hope of success. The use of penicillin has not yet been sufficiently explored.[22] Its use in a case of acute hemolytic *Staphylococcus albus* endocarditis in a 23-year-old woman by one of us (F. D. Z.) produced only temporary improvement in the clinical picture, and during a short period the blood became sterile. At post-mortem examination there was no evidence that the pathologic process had been affected.

Two reports reveal results that are encouraging. The Alexanders[23] report the cure of an acute *Streptococcus hemolyticus* endocarditis in a man aged 62 years. The diagnosis was based on the changing character of the heart murmurs, the positive blood cultures, and the patient's septic temperature curve, in absence of other foci of infection. Sulfanilamide was given in doses of 15 grains (1 Gm.) every four hours for a period of six weeks.

Blumberg, Heine, and Lipshutz[24] report recovery from pneumococcus, Type XXVIII, endocarditis in the case of an 18-year-old man who was treated with sulfadiazine, sulfathiazole, and type-specific antipneumococcus serum. These authors have reviewed the literature and report two other cures of pneumococcus endocarditis.

many of the diagnostic difficulties. The keenest discrimination is required to avoid misplacing clinical emphasis. In many of the cases reported, the urgency of certain aspects, such as diabetic acidosis, tended to distract attention from the problem as a whole.

Table I shows that five cases occurred in the seventh decade of life, and two each in the eighth and ninth. The striking difference in sex incidence (six females to three males) is not easily explained. It may well be due only to the small number of cases, but it should be considered along with other well-known sex differences of later life, such as the greater longevity, the lower incidence of arteriosclerotic heart disease and malignant neoplasms, and the greater mental stability, of the aged female.

Among the conditions arising to confuse the clinician in these cases may be noted the difficulty in the interpretation of the cardiac manifestations. In old patients with frank chronic valvular disease, even more often than with the young, no history of previous heart disease or of attacks of rheumatic fever can be elicited, and such was the case here. Yet, as has been shown in the discussion of the pathologic changes, in four, and possibly five, of nine cases there were definite old valvular lesions, presumably of rheumatic origin. Only one patient showed definite arteriosclerotic valvular changes. If we review the clinical records, we find that in three of the four cases of proved rheumatic disease there were harsh systolic murmurs, either at the mitral or aortic areas, or these murmurs were loud over the entire precordium. In the remaining rheumatic case the only observed cardiac abnormality was the occurrence of extrasystoles. In Case 5 a harsh systolic murmur was audible, and, at autopsy, fibrosis of the myocardium due to arteriosclerotic narrowing of the coronary arteries and dilatation of all the heart chambers were found. It is clear that the interpretation of the auscultatory phenomena in these ailing old people presents great difficulties. In general, we believe that systolic cardiac murmurs in the aged may be due to rheumatic valvular deformities, arteriosclerotic valvular lesions, including calcification of the valves and of the mitral ring (not observed in the present series), and to cardiac dilatation. Systolic murmurs which appear acutely may be caused by perforation of a valve cusp or by rupture of a papillary muscle. The differentiation is impossible without careful study of both the history and the physical signs, plus the aid of the roentgenologic examination, which may be used to detect valvular deposits of calcium, as well as variations in the size of the heart. These observations refer largely to involvement of the mitral valve. Lack of space precludes discussion of the signs of aortic stenosis, either with or without calcification—a lesion that is far from rare in the aged and which has been thoroughly discussed by many writers in the past ten years. That no change in the character of the heart sounds and murmurs in this series of cases was noted means only that insufficient attention was paid to this point.

Since in cases of both acute and subacute bacterial endocarditis, clinicians have long been trained to look for embolic skin lesions, their occurrence in this series deserves discussion. In Case 4, petechiae were noted after an eruption thought to be due to sulfonamides had subsided. In Case 6 a large subconjunctival hemorrhage appeared once during the course of the disease. In Case 8 a tender red area was noted on the right big toe, and a similar area of redness over the right external malleolus occurred in Case 9. It is our belief that the paucity of embolic skin lesions is to be ascribed to faulty observation, rather than to any peculiarity in the disease or to the age of the patients. These manifestations must be looked for daily and with meticulous care. The petechiae in subacute bacterial endocarditis may be very elusive even in clear-cut cases. It

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AURICULAR HEART SOUNDS IN AURICULAR FLUTTER

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Soon after the recognition of auricular flutter as a clinical entity, Cohn[1] stated that auricular sounds may occasionally be heard in this condition. Passing mention of auricular sounds in flutter has been made by others from time to time. The first graphic recording was that of Bennett and Kerr,[2] published in 1932. Four additional cases, complete with phonocardiograms, have been reported,[3-6] and one tracing has been published without any clinical information.[7, 8] Two other cases have been reported in which the fluttering auricle appeared to influence the intensity of the first ventricular sound.[9]

We have observed two cases of auricular flutter in which loud clicking sounds were associated with the flutter movement of the auricles. The sounds were transmitted to areas different from those hitherto described; their relation to the state of the myocardium and their position in the cardiac cycle were unusual. A discussion of our cases in relation to those observed by others, and of the probable factors responsible for auscultatory phenomena of this type appears justified. Table I summarizes the pertinent observations in the eight previous cases and in the two reported in this communication.

CASE REPORTS

Case 1.—A 40-year-old riveter entered the hospital Jan. 17, 1944, complaining of shortness of breath and swelling of the ankles and abdomen for about three weeks. There was no history of previous heart disease or of rheumatic infection. Physical examination revealed a very obese, white man who was moderately dyspneic, cyanotic, and very edematous. The retinal arterioles were normal, and there was no evidence of hypertensive or arteriosclerotic retinopathy. The neck veins were markedly distended, but exhibited no pulsations. There were physical and roentgenologic signs of marked pulmonary congestion and edema. There was generalized cardiac enlargement, and the cardiothoracic ratio was 60 per cent. No murmurs were heard. The rhythm was regular, and the rate was constant at 150 beats per minute, suggesting auricular flutter or auricular paroxysmal tachycardia. The blood pressure was 110/70. Shifting dullness was noted in the abdomen, and no masses could be felt. Four plus edema was present in both lower extremities.

The patient was placed on a strict cardiac regimen consisting of rest in bed, oxygen, a salt-free diet, and large doses of digitalis. Abdominal paracentesis, ammonium chloride,

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Received for publication Aug. 17, 1944.
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These good results make it obligatory for physicians who are treating acute bacterial endocarditis in any age group to use sulfonamide drugs, penicillin, and specific antisera if possible. In addition, no reasonable surgical effort to eradicate or to drain the primary focus of infection should be omitted. In cases of superficial thrombophlebitis, ligation of the vein above the affected area is theoretically justified, but is of little value if a secondary focus on a heart valve has already been established.

Hamburger and his collaborators[25] have reported the case of a Negro woman, aged 43 years, "with an ultimately fatal Type VII pneumococcus endocarditis treated with sulfapyrazine intermittently over a period of six months. The pneumococci isolated at intervals during this treatment period showed progressive increase in sulfonamide resistance." They point out that this is a serious complication in the long-continued use of sulfonamides.

SUMMARY

In an effort to clarify the disease pictures encountered in the aged, nine cases of acute bacterial endocarditis, with autopsy, have been reported among patients whose ages ranged from 60 to 80 years. In none of these cases was the diagnosis made clinically. The bacteriologic, pathologic, and clinical features are discussed, and it is pointed out that the diagnosis is obscured by the multiplicity of symptoms and signs, as well as by the prostration of the patient. It is believed that these cases will be detected more often if the possibilty of this complication is borne in mind, especially when positive blood cultures are found in old people, and even in cases in which the diagnosis seems to be obvious. Clarification of the clinical problems posed by the aged patient offers many fascinating opportunities to the discerning physician.

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TABLE I. AURICULAR SOUNDS RECORDED IN AURICULAR FLUTTER*

NO.	AUTHORS	AGE	SEX	DIAGNOSIS	CARDIAC FAILURE	A-V RATIO	AURICULAR RATE	VENTRICULAR RATE	POSITION OF AURICULAR SOUND	TIME RELATION	REMARKS
1.	Bennett and Kerr, 1932[2]	–	–	–	–	Irregular ventricular response: 2:1, 3:1	270	102	Third intercostal space to left sternal border	Auricular sounds coincide with first and second ventricular sound and intensify the latter	The auricular sounds alternating in intensity following carotid sinus pressure; auricular electric alternans
2.	Cossio and Fongi,† 1936[7]	–	–	–	–	Complete A-V heart block	250	33	–	No systolic auricular sounds	–
2a.	Taquini‡[8]	–	–	–	–	Complete A-V heart block	220	33	–	Esophageal auricular sounds present in systole and diastole	Simultaneous sound-records from precordium and esophagus
3.	Routier, Mamon, and Lemant, 1936[9]	66	male	Atherosclerotic heart disease, Adams-Stokes seizures	Present	Complete A-V heart block	274	32	–	No auricular sounds, but change in intensity of first ventricular sound	
4.	Routier, Mamon, and Lemant, 1936[9]	52	male	Atherosclerotic heart disease, angina pectoris	Absent	Complete A-V heart block	?	36		As No. 3	

and mercupurin were used to effect diuresis. Thiamine chloride was given in a dose of 60 mg. daily during the first week and 10 mg. daily thereafter because of the possibility of beriberi heart disease. However, no definite evidence was elicited to confirm the suspicion of beriberi.

On the seventh hospital day, after a total of 3.2 Gm. of digitalis leaf orally and 7 c.c. of cedilanid intravenously, the patient's general condition had improved somewhat, but signs of right ventricular failure were still present. The heart rate remained at 144 beats per minute, and could not be influenced by carotid sinus pressure. On the afternoon of the seventh day, and for the first time during his hospital stay, distinct, loud, and rapid clicking sounds were heard over the base, particularly in the second and third intercostal spaces at the left sternal border. Two of these sounds were heard during each cycle. With progressive digitalization, the ventricular rhythm became irregular and then regular, at a rate of about seventy beats per minute. At this time, the rate of the clicking sounds was approximately triple the ventricular rate. These extra sounds were heard consistently between the seventh and twentieth hospital days, except on the fourteenth day, when transient auricular fibrillation was present (confirmed by an electrocardiogram). The rhythm subsequently reverted to flutter and the extra sounds returned. The sounds varied in intensity and seemed particularly loud shortly after the intravenous injection of cedilanid. Between the seventh and twentieth hospital days, the patient lost a total of 55 pounds, and the heart became fully compensated. On the twentieth hospital day, after the patient had received a total of 7.7 Gm. of digitalis orally and 18 c.c. of cedilanid intravenously, normal sinus mechanism was re-established. The extra sounds over the base disappeared and did not return.

The patient was discharged Feg. 14, 1944, on a maintenance dose of digitalis, with the final diagnosis of paroxysmal auricular flutter with regular and irregular ventricular responses, cause unknown. A rheumatic valvular heart lesion was suspected, but could not be proved on clinical or roentgenologic examination.

Three weeks after the patient's discharge from the hospital, while changing a tire on his car, he was suddenly seized with extreme dyspnea, and died a few hours later. The heart was obtained after the body had been embalmed, and was examined by Dr. Bert Stofer. It revealed generalized enlargement, weighing 620 grams. The ratio of left to right ventricular weights was 1.5:1. This is within the normal range, and indicates that the left and right ventricles were proportionally hypertrophied.[11] The coronary arteries were patent throughout, and showed minimal sclerotic changes. There was no evidence of myocardial infarction. The endocardium and pericardium were normal. Sections of the ventricles and auricles were negative except for hypertrophy. Since no other tissues were examined, a pre-existent hypertension could not be excluded with certainty. The cause of the cardiac hypertrophy remained undetermined.

CASE 2.—A 36-year-old Negro housewife entered the hospital Sept. 1, 1943, with a history of repeated attacks of rheumatic fever since 1926, orthopnea and peripheral edema since April, 1943, and cough, fever, hemoptysis, and left-sided pleuritic pain of three days' duration. Physical examination revealed marked orthopnea, moderate cyanosis, slight jaundice, and 3 plus edema of the lower extremities. The blood pressure was 130/90. The jugular veins were markedly distended, and exhibited a strong, positive venous pulse. A large pleural effusion occupied the lower two-thirds of the left hemithorax. The apical impulse was barely palpable in the fifth intercostal space, 9 cm. to the left of the midline. The left border, by roentgenogram, was approximately 10.5 cm. to the left, and the right border was 9.5 cm. to the right, of the midline. The results of percussion and fluoroscopic examination were indicative of pericardial effusion. During the first week of hospitalization a loud pericardial friction rub was heard over the precordium to the left of the sternum, and a pleural rub was heard in the left axilla. In addition, there were endocardial murmurs which were identified after the disappearance of the rub as a to-and-fro basal murmur typical of aortic insufficiency. The rhythm was regular and the ventricular rate was consistently around 80 per minute. In the second and third intercostal spaces to the right of the sternum, a rapid, regular, slapping impulse could be distinctly felt at a rate approximately three times the ventricular rate. Corresponding with these palpable impulses, three loud clicking sounds were heard in each cycle, in addition to the to-and-fro blowing murmur of aortic insufficiency. These impulses and sounds were present throughout her hospital stay and were recorded graphically. A diagnosis was made of acute rheumatic pancarditis with 3:1 auricular flutter, complicating chronic rheumatic aortic and mitral valvulitis. The patient remained in the hospital for eighteen days and improved somewhat as a result of the administration of digitalis and diuretics. She refused thoracentesis and left the hospital against advice.

Six months later, after a period of almost complete rest in bed, a salt-poor diet, and digitalis medication at home, she was readmitted with a left-sided empyema which was drained surgically. Her cardiac condition had greatly improved. There was no trace of edema, very little dyspnea, and no orthopnea. The rhythm was completely regular, slow, and of sinus origin. The murmurs over the heart were similar to those observed before, suggesting a combined aortic and mitral valvulitis. The extra sounds and impulses formerly heard over the base of the heart had entirely disappeared.

Electrocardiograms.—Standard bipolar limb leads and standard unipolar precordial leads were recorded in both cases. In addition, unipolar limb leads (extremity potentials) and serial unipolar esophageal leads were obtained in the second case.

TABLE II. CASE 1. CYCLIC VARIATIONS OF THE AURICULAR SOUND (IN SECONDS)

AURICULAR SOUNDS				CORRESPONDING FLUTTER CYCLE (ECG)			
A	B	C	D	A	B	C	D
0.278	0.192	0.219	0.222	0.237	0.222	0.224	0.232
0.278	0.183	0.218	0.225	0.234	0.222	0.234	0.226
0.274			0.226	0.227			0.227
0.316	0.212	0.240	0.252	0.251	0.257	0.246	0.255
0.279	0.213	0.242	0.244	0.245	0.243	0.242	0.249
							0.248
0.276	0.180	0.199	0.224	0.225	0.219	0.234	0.227
0.282	0.187	0.211	0.225	0.225	0.224	0.223	0.226
	0.182	0.213	0.212		0.229	0.222	

A = Interval between systolic and first diastolic sound.
B = Interval between first diastolic and second diastolic sound.
C = Interval between second diastolic and first ventricular sound.
D = Interval between first ventricular and systolic auricular sound.

Note: Each group of figures represents measurements from one strip of film (enlarged photographs). Note the increase in time in *A* and the corresponding decrease in *B* in all instances of the sound measurements, without identical changes in the corresponding flutter cycle from the electrocardiogram.

The first record in Case 1, taken on the day of admission, revealed classical auricular flutter with a perfect 2:1 ventricular response (ventricular rate, 136, auricular rate, 272). The QRS complexes were upright in Leads I and II and of a vibratory type in Lead III. T waves were not discernible in the standard leads. Serial precordial leads (V_2, V_4, and V_6) were compatible with left ventricular enlargement. On the day the extra sounds were first noted a 2:1 response was present. On the following day the ratio had changed to 4:1 (auricular rate, 259, ventricular rate, 65). On the fourteenth hospital day, auricular fibrillation was recorded, with an irregular ventricular response. Left axis deviation was present (α = minus 18 degrees), and a U-shaped S-T depression was noted in standard bipolar limb leads and in precordial leads (digitalis medication). On the twentieth hospital day a record was obtained which for the first time revealed normal sinoauricular rhythm, with a heart rate of 79 beats per minute and a P-R interval of 0.24 second. The P waves were markedly split in Leads I and II, and biphasic in Lead V_1. The QRS and T waves appeared similar to those recorded on previous occasions. Late records taken on the twenty-fourth and on the twenty-ninth hospital days were similar except for the P-R interval, which gradually returned to normal values. Measurements of the rate of the flutter cycle taken from enlarged photographs and obtained with a Lucas comparator* revealed an average variation of the individual flutter cycles of 0.0065 second (0 to 0.0150 second) (Table II).

All records in Case 2 during the patient's first stay in the hospital revealed pure auricular flutter with a 3:1 ventricular response (auricular rate, 230, ven-

*Permission to use the comparator of the Heart Station of the University Hospital in Ann Arbor, Michigan, was given by Dr. F. N. Wilson, whose kindness is gratefully acknowledged.

5. Ludwig and Bener,§ 1936[3]	40	male	Syphilitic heart disease, aortic insufficiency, pericarditis	Present	Complete A-V heart block	250	40	Second and third intercostal spaces left sternal border	No systolic auricular sound	Auricular sounds disappear with compensation: *flutter gallop.* Autopsy revealed pericardiosternal adhesions
6. Lian and Welti, 1938[4]	48	female	Hypertensive heart disease	Present	Complete A-V heart block	270?	45	Apex	No systolic auricular sound; reduplication of second ventricular sound	Auricular sounds disappear with compensation: *flutter gallop*
7. Calo[5]	23	female	Rheumatic heart disease	Present	Irregular ventricular response: 3:1, 4:1	300	75	Entire precordium		Auricular sounds disappear with compensation: *flutter gallop*
8. González Sabathié, Gaspary, and Voogd, 1942[6]	70	male	Hypertensive heart disease	Present	Complete A-V heart block	250	28	Midprecordial region	No systolic auricular sounds	
9. Hecht and Myers, 1944	40	male	?	Present	Response: 2:1, 3:1, 4:1	259	65	Second intercostal space and along left sternal border	Auricular sounds late in systole and in diastole	Loudest during recovery from cardiac failure. Auricular sounds slightly irregular and influenced by cardiac systole
10. Hecht and Myers, 1944	36	female	Rheumatic heart disease, pancarditis	Present	Response: 3:1	230	75	Second and third right intercostal spaces	Loudest auricular sound in systole	Auricular sounds slightly irregular and influenced by cardiac systole

*Two cases of auricular flutter have been reported by Laubry, Routier, and van Bogaert (Arch. d. mal. du coeur 25: 321, 1935). From the observations presented it seems likely that auricular sounds were present, but no phonocardiographic tracings were made. Brief mention has occasionally been made of other cases, but since no clinical data or tracings are available, they have not been included in the present report. Reference made by a recent monograph[10] to auricular sounds in flutter reported by Roch, Scelounoff, and Duchosal (Bull. et mém. Soc. méd. hôp. de Paris 50: 1335, 1934) is erroneous because the sounds observed were caused by normal auricular complexes in complete A-V heart block in a patient suffering from attacks of 1:1 and 2:1 auricular flutter.

†Their tracing is reproduced in *The Heart Sounds in Normal and Pathological Conditions* by Orias and Braun-Menéndez,[10] p. 184, Fig. 91.

‡From the electrocardiogram it appears likely that this case is the same as that of Cossio and Fongi. Taquini's tracing, however, is obviously a different recording. No clinical data are available in either communication. The record of Taquini is included, for his observations on esophageal sounds are of considerable theoretical significance.

§Autopsy observations in this case are discussed by Ludwig.[11]

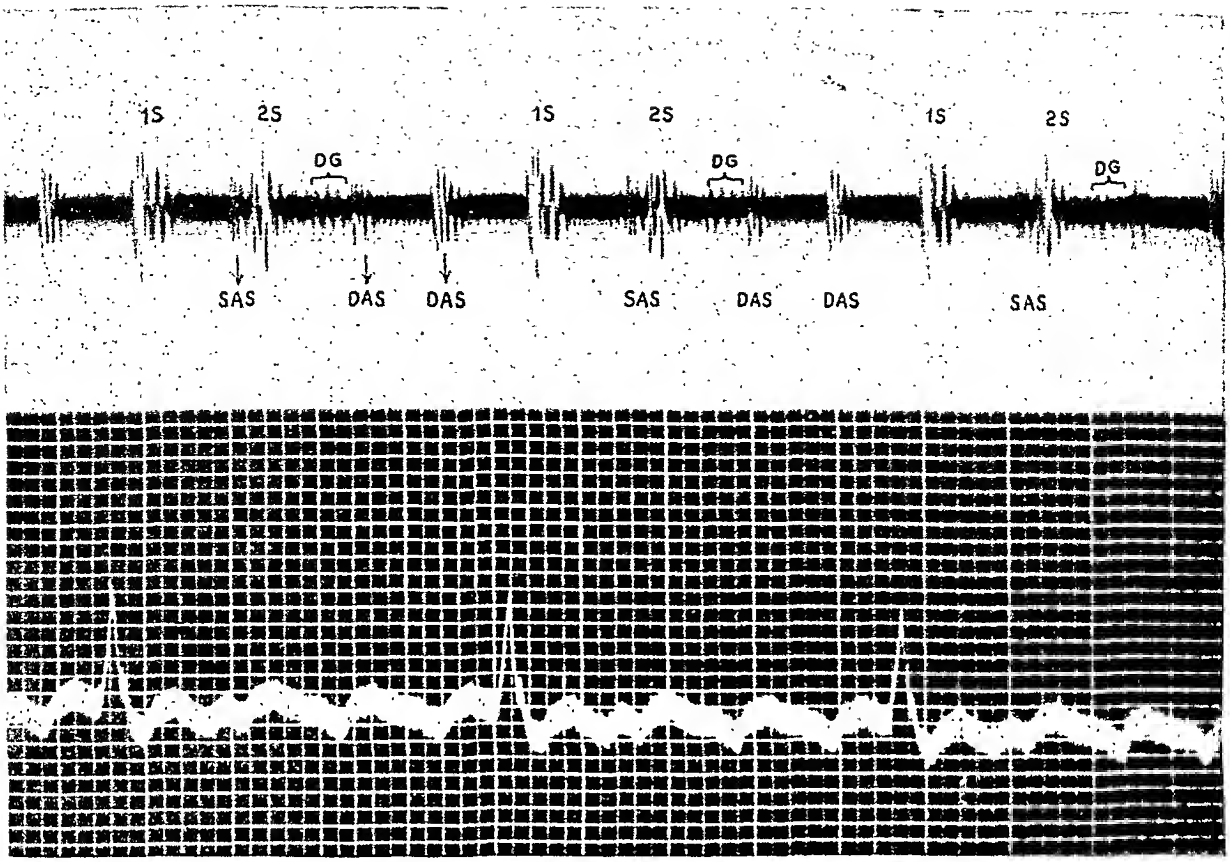

Fig. 1.—Case 1. Upper tracing: Sound records taken over second intercostal space, left sternal border. Lower tracing: Simultaneously recorded electrocardiogram. Lead II. *SAS* and *DAS*, auricular sounds; *1S* and *2S*, ventricular sounds; *DG*, protodiastolic gallop sound.

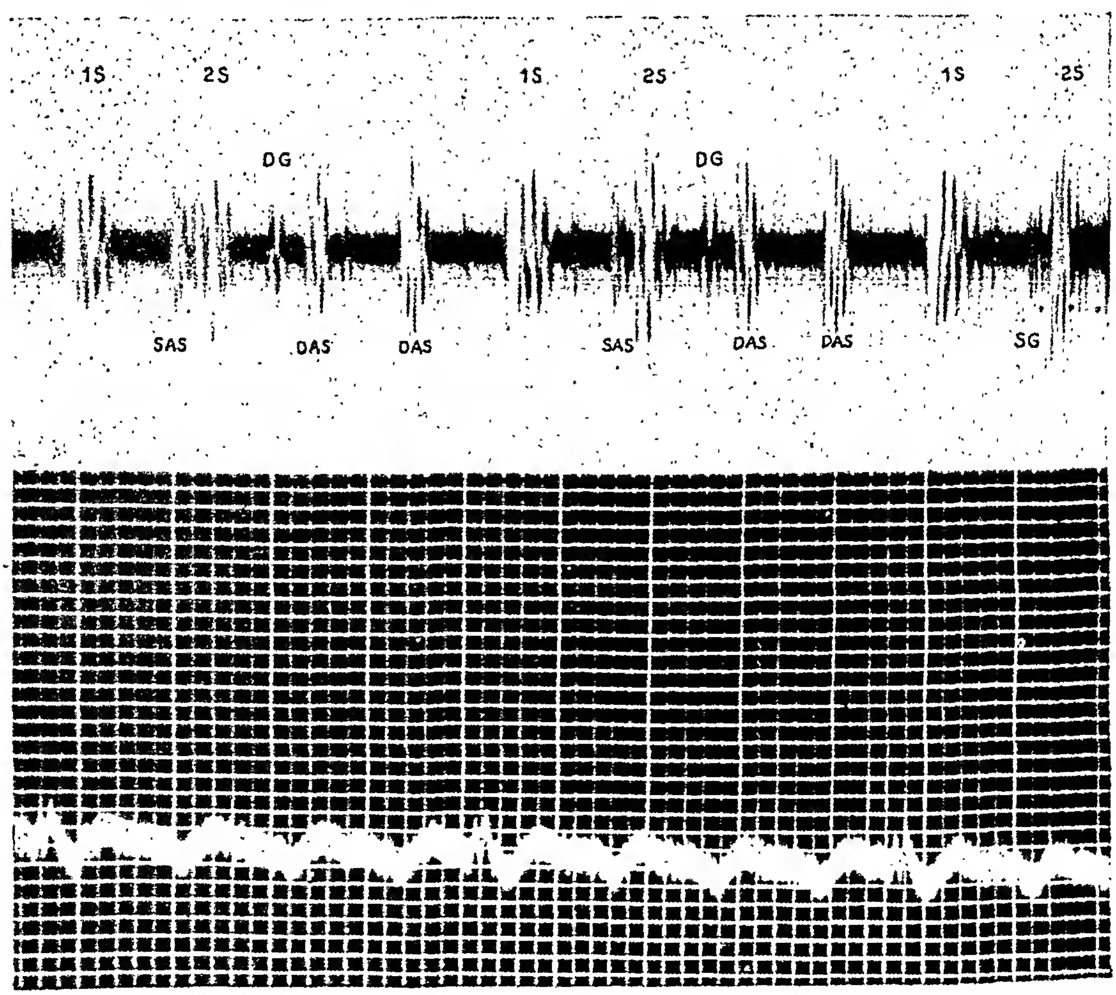

Fig. 2.—Case 1. Upper tracing: Sound records taken over second intercostal space, left sternal border. Lower tracing: Simultaneously recorded electrocardiogram, Lead III. *SAS* and *DAS*, auricular sounds; *1S* and *2S*, ventricular sounds; *DG*, protodiastolic gallop sound.

tricular rate, 75). The QRS measured 0.07 second. Splintered initial ventricular complexes were present in Lead III. T waves could not be identified in any of the standard limb leads. Unipolar limb leads (extremity potentials) suggested a semivertically placed heart.[12] Unipolar leads taken over the second, third, and fourth intercostal space near the right sternal border and over the ensiform process (V_E) revealed small R waves and split S waves. A normal QRS pattern was present in standard precordial Leads V_2 to V_6. A U-shaped depression of the S-T segment, with inversion of T, was best seen in V_2, but occurred in other leads as well. These T-wave changes were thought to be caused in part by digitalis therapy. The flutter cycles were extremely constant, with an average variation of 0.009 second (0.002 to 0.022 second). When the patient returned several months later, normal sinus mechanism was present, with a heart rate of 88 beats per minute. The P-R interval measured 0.19 second. There was little change in the QRS and T waves. The P waves were unusually large and broad, particularly in Leads I and II. Standard precordial leads showed biphasic P waves in V_1, and serial unipolar esophageal leads from the auricular level showed P waves over twice the size of the corresponding QRS deflection. There was a late intrinsicoid auricular deflection. The auricular changes in standard bipolar and in serial unipolar leads were diagnostic of left auricular enlargement.[13] Unipolar extremity potentials suggested that the heart was more vertically placed than on previous examinations. On one occasion a transient A-V nodal rhythm was present.

Sound Records.—Sound records were obtained in the first case with the stethograph attached to the Cambridge Hospital model. A nonlogarithmic microphone was used. In the second case the sounds and impulses were registered with a Sanborn Tribeam electrocardiograph. A special chest piece was used, which allowed simultaneous registration of the sounds and of the mechanical impulses from the same area (linear and stethoscopic phonocardiograms). The chest piece was equipped with two outlets. One was connected to a crystal microphone of a logarithmic type for the recording of sounds, the other to a piezoelectric transducer for graphic registration of the mechanical vibrations of the chest wall. The arrangement has been described by Rappaport and Sprague.[14] Using a Lucas comparator, analyses of the time relations were made from the tracings and from enlarged photographs.

In the first case, it was noted that, when the microphone was placed over the area of maximal intensity of the abnormal sounds, six, instead of the usual two, heart sounds were present (Figs. 1 and 2). The first ventricular heart sound appeared to be markedly accentuated. The second sound seemed reduplicated, but close analysis revealed that the apparent splitting was due to an extra sound (*SAS*) which preceded the second ventricular sound by 0.055 second. This extra sound consisted of a few sharp vibrations of high frequency. Following the second sound at an interval of 0.13 second, a few low-pitched vibrations were noted; their character, frequency, and time relationship to the second sound suggested a protodiastolic gallop sound (*DG*). Two additional sounds were recorded in diastole (*DAS*), which not only were similar to one another in frequency, intensity, and duration, but also resembled closely the systolic extra sound (*SAS*) described above. If it is assumed that another extra sound coincided with the first ventricular sound and contributed to its unusual intensity, four extra sounds were present during each cycle: one buried in the first ventricular sound, one shortly preceding the second sound, one in early diastole, and one in mid-diastole. These four extra sounds corresponded with the four flutter waves of the simultaneously recorded electrocardiogram.

TABLE III. CASE 2. CYCLIC VARIATIONS OF THE AURICULAR SOUNDS (IN SECONDS)

AURICULAR SOUNDS			CORRESPONDING FLUTTER CYCLE (ECG)		
A	B	C	A	B	C
0.262	0.260	0.236	0.257	0.250	0.254
0.275	0.264	0.246	0.260	0.250	0.252
0.262	0.259	0.233			
0.272	0.254	0.232	0.262	0.254	0.244
0.276	0.263	0.244	0.260	0.253	0.263
0.262			0.260		
0.292	0.279	0.276	0.294	0.316	0.296
0.291	0.292	0.278	0.305	0.302	0.294
0.274	0.286	0.297	0.314	0.295	
0.276	0.246	0.233	0.252	0.257	0.246
0.264	0.246	0.251	0.258	0.254	0.245
	0.248				

A = Interval between systolic and first diastolic sound.
B = Interval between first diastolic and second diastolic sound.
C = Interval between second diastolic and systolic sound.
See note to Table II. Relatively little variation in cycle length is noted in the first and third group. Measurements on a number of other film strips were essentially similar to the one here represented.

appeared loudest, and were also obtained from several other points over the precordium. Over the first aortic auscultation point, a simultaneous recording was made of mechanical vibrations and sound effects with the electrocardiogram (Fig. 4). The analysis of the simultaneously recorded electrocardiograms and sound and pulse records was facilitated when the speed of the recording film was increased from the usual 25 to 75 mm. per second. It gave the following results:

The flutter waves of the electrocardiogram showed a fairly constant rate of 330 per minute. Occasionally slight slowing was demonstrable during systolic ventricular contraction (Table III), but accurate measurements were made difficult by the continuous movement of the string and the absence of sharp end points.

Five mechanical vibrations were recorded. Two apparently coincided with the first and second ventricular sound and were of lower voltage than the remaining three, which appeared evenly spaced, one in systole (following the QRS complex by 0.4 second), and two in diastole. Again there was a slight increase in the interval between the systolic and the first diastolic thrust, and a corresponding decrease in time between the first and second diastolic beat.

Sound records over the same area (second and third right intercostal space at right sternal border) (Figs. 3 and 4) showed a loud, low-pitched systolic murmur (*SM*). In some of the records, particularly when the two-outlet chest piece was employed (Fig. 4), the murmur tended to obscure the first ventricular sound (filter effect). Late in systole a loud snapping sound was present, usually the loudest sound of the cycle (*SAS*). This sound was followed by the second ventricular sound (*2S*) by about 0.08 second. The second sound led into a short, relatively high-pitched, decrescendo type of diastolic murmur (*DM*). Two extra sounds were noted in diastole. One of them appeared in early diastole (*DAS*) and was usually somewhat less intense than either the systolic extra sound or the second ventricular sound. The second diastolic extra sound appeared in presystole (*PAS*) and was usually fainter than any of the other sounds recorded. The three extra sounds, two in diastole and one in systole, were much alike. They were of short duration, rarely exceeding 0.04 second. With the technique employed, they showed not more than about three to four rapid oscillations of relatively high amplitude, which was strikingly different from the pattern usually noted in "normal" auricular sounds or au-

The diastolic extra sounds coincided with the trough of the flutter wave in the electrocardiogram. The trough also coincided with the first ventricular sound and immediately preceded the second ventricular sound. Assuming an extra sound superimposed upon the first ventricular sound, the four extra sounds would occur with regularity at about the same time in the flutter cycle of the electrocardiogram. They were almost equally spaced, and the assumption that these sounds were linked to the auricular contraction can hardly be questioned. With the establishment of normal sinus rhythm, the accentuation of the first ventricular sound, the extra sound in systole, and the two diastolic sounds were no longer present.

Fig. 3.—Case 2. Upper tracing: Sound records taken over second intercostal space, right sternal border. Lower tracing: Simultaneously recorded electrocardiogram, Lead III. *SAS, DAS*, and *PAS*, auricular sounds; *2S*, second ventricular sound (first sound buried in murmur *SM*); *SM—DM*, to-and-fro murmurs of aortic insufficiency. Note that there are five heart sounds and two murmurs per cycle.

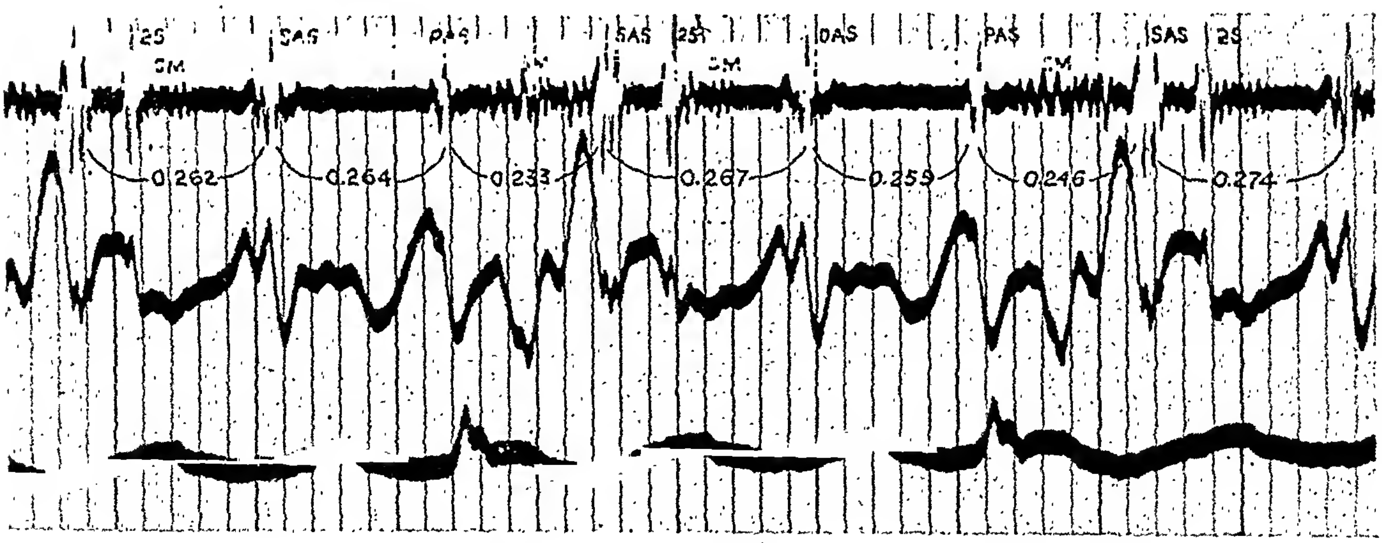

Fig. 4.—Case 2. Upper tracing: Sound records taken over second intercostal space, right sternal border. Middle tracing: Impulses over the same area. Lower tracing: Simultaneously recorded electrocardiogram, Lead III. *SAS, DAS, PAS*, auricular sounds, *2S*, second ventricular sound (first sound buried in murmur *SM*). *SM-DM*, to-and-fro murmur of aortic insufficiency. Intervals between auricular sounds in seconds.

Accurate measurements of the interval between the extra sounds revealed distinct differences which were apparently dependent on the state of ventricular contraction. The time between the systolic and the first diastolic extra sound was invariably longer than the time between the first and second diastolic sounds, or, in other words, the first diastolic extra sound appeared delayed. In contrast, the differences between the second diastolic and the first ventricular sound and between the first ventricular sound and the systolic extra sound were infinitesimal (Table II).

Phonocardiographic tracings in the second case were taken from the second and third intercostal spaces at the right sternal border, where the extra sounds

activity of the auricles became apparent by a change in the intensity of the first ventricular sound, which appeared loudest when the crest of the flutter wave preceded the onset of QRS by about 0.08 to 0.12 second. One is inclined to assume that the change in intensity of the first ventricular sound in their cases was at least in part caused by the influence of auricular contraction on the wave of ventricular filling and on the position of the atrioventricular valves.

Auscultatory phenomena directly or indirectly related to the auricle tend to become intensified in the failing heart, and may be manifested by gallop rhythm over the ventricle; this is customarily explained by the inrush of blood pounding against the ventricular walls.[10]

In three of the cases included in Table I, the extra sounds were heard during heart failure and disappeared with compensation, despite the presence of flutter. In two of these cases, the extra sounds were best heard at the apex, suggesting a ventricular origin. The location of the sounds in these cases and the apparent relation to the functional state of the heart muscle justified the term "flutter gallop" in instances of this kind. This phenomenon could not account for the extra sounds in our cases for the following reasons: (1) The sounds were picked up at the base rather than at the apex; (2) One of the sounds occurred during ventricular systole at a time when the atrioventricular valves were closed.

Our cases are the only ones on record in which auricular sounds of the fluttering auricle could be registered from the precordium during ventricular systole. Loud auricular sounds beginning before, but ending during, the earlier part of ventricular systole have been recorded through a microphone placed in the esophagus.[8, 20, 21] Using such a microphone, systolic auricular sounds have been observed in cases of atrioventricular dissociation,[8] and Taquini has published an esophageal phonocardiogram in a case of auricular flutter in which sounds synchronous with the flutter waves were present in ventricular systole as well as during diastole. Although it has been accepted that sounds caused by muscular contraction of the auricles can be recorded from the esophagus, many investigators contend that such sounds cannot be registered from the precordium, and have assumed that precordial sounds associated with auricular activity are not produced in the auricles, but are set up secondarily in the atrioventricular valves or in the ventricles.[7, 8, 10, 22-27] The fact that, in both of our cases, loud sounds synchronous with auricular activity were recorded over the base during ventricular systole is against the foregoing hypothesis.

The extra sounds in our two cases differed in several respects from the sounds reported in the other eight cases of flutter, as well as from the auricular sounds in normal sinus rhythm. Sounds directly or indirectly resulting from auricular contraction are usually heard best over the midprecordium or at the apex (i.e., in the direction of blood flow), rather than at the pulmonary or aortic auscultation points, as in our cases. The usual auricular sounds are much less intense and differ strikingly in pitch and quality from the clicking sounds present in our cases. These differences are also apparent in the phonocardiographic records.

In view of the known pericarditis in Case 2, an auricular friction rub was considered. However, the auscultatory and phonocardiographic characteristics of the sounds in these cases differed markedly from the auricular friction rub described by others.[28]

The coincidence of the extra sounds in our cases with the trough of the flutter waves in the electrocardiogram indicates that they were related in some

ricular sounds observed in atrioventricular block. Again the three sounds were not spaced evenly: the first diastolic sound appeared to be delayed in some, but not in all, of the records obtained (Table III).

The mechanical impulses recorded seemed to precede the sounds by a fraction of a second (Fig. 4). Both sounds and impulses occurred during the dale of the flutter wave in a simultaneously recorded Lead III. The over-all frequency of these extra sounds and its mechanical corollary coincided very closely with that of the fluttering auricle, for the delay of the first diastolic sound was made up by a slight shortening of the interval from the first to the second diastolic sound (Fig. 4, Table III). The sounds disappeared after normal sinus rhythm had been re-established. It seems certain that the extra sounds and impulses recorded were closely related to the flutter movement of the auricles.

DISCUSSION

Electrophysiologically, auricular flutter and auricular fibrillation have a fundamentally similar mechanism. In both, a continuous wave of excitation travels in a strip of muscle around one or two of the large venous openings (mother wave) and gives rise to tangential offshoots which reach the A-V node at regular or irregular intervals. Minor differences in the speed and pathway of the excitation wave and in the responsiveness of auricular muscle determine whether auricular fibrillation or flutter is present. Mechanically, the differences between auricular flutter and auricular fibrillation are pronounced and fundamental. Auricular fibrillation consists of incoordinate tremulations of auricular muscle which are incapable of properly filling the ventricular cavities at any time. Auricular flutter consists of rapid but rhythmic and coordinate contraction of auricular muscle, as has been demonstrated clinically by careful fluoroscopic examination with or without the aid of barium in the esophagus.[15, 16] Coordinate contractions in auricular flutter have also been demonstrated by the roentgenkymograph.[17]

Thus, conditions for the production of sounds from the auricles, namely, muscular contraction and propulsion of blood, are present in auricular flutter but are absent in auricular fibrillation. Auricular sounds have never been observed, and are inconceivable, in auricular fibrillation. There seems to be no doubt that the fluttering auricle was in some way responsible for the extra sounds recorded in our two cases, as well as in the others summarized in Table I.

The extreme rarity of audible auricular sounds in flutter is not unexpected when the incidence of audible auricular sounds in normal hearts beating in sinus rhythm is taken into consideration. The sound of the normal auricular contraction is so low in intensity and pitch and so near the first ventricular sound that it is ordinarily inaudible. Even when the auricular and ventricular contractions are widely separated by a conduction defect, the auricular sounds are not easily heard. The prolonged diastolic silence in auriculoventricular block apparently facilitates detection of sounds from the fluttering, as well as from the normally contracting, auricle. Four of the patients in Table I had auricular flutter and complete auriculoventricular block, a rare combination of cardiac irregularities.[18, 19] Auricular sounds, with sinus mechanism, which are below the threshold of the human ear are frequently recordable by phonocardiogram ("subsonic" auricular sounds). It is possible that routine phonocardiograms in cases of auricular flutter would reveal that auricular sounds are more common than has hitherto been supposed.

The cases of Routier, Mamou, and Lemant[9] had atrioventricular heart block and auricular flutter, but no direct auricular sounds. The rhythmic

3. Two alternate explanations are offered for the sounds observed: The flutter contractions of the auricles may have been audible because of their unusual forcefulness, or an "auricular click" associated with pleuropericardial adhesions may have been present.

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way to the flutter movement of the auricles. The ability to palpate and graphically record an impulse coincident with the extra sounds and flutter wave in Case 2 would suggest that the contractions of the fluttering auricles were exceptionally strong, perhaps sufficient to account for the unusual quality and intensity of the sounds. The location of the sounds and impulses in the second intercostal space on the right may have been due to cardiac displacement or to transmission from the right auricle into the superior vena cava. The fact that the extra sounds in Case 1 became distinctly louder shortly after the intravenous injection of cedilanid also suggests a possible relationship between the strength of the muscular contraction and the intensity of the sounds. However, this explanation does not account for the delayed appearance of the auricular sound located in early diastole. The interval between the auricular sound which fell during ventricular systole and the next auricular sound in protodiastole was often, although not always, distinctly longer than the intervals between any other pair of auricular sounds. This was observed in both cases and has not been noted before.

The postsystolic delay, together with the clicking quality and unusual loudness of the sounds associated with the flutter movement, raises the question whether they were extracardiac in origin, i.e., possibly caused by adhesions drawn taut by the flutter contractions. The apparent forcefulness of the auricular beats in both cases would also support this explanation, as does their increase in intensity following the intravenous administration of digitalis. "Systolic ventricular clicks" are aggravated by increasing the force of ventricular contraction.[29] The delay in the sound which followed ventricular systole might be explained by the change in position of the heart associated with ventricular contraction. The character of the sounds resembled the "systolic ventricular click" which has been reported in association with pleuropericardial adhesions.[29-32] Assuming an "auricular click" as the cause of the sounds observed, it should be noted that pleurisy and pericarditis were present in Case 2 at the time the auricular sounds were heard. Extensive pericardial adhesions were found at autopsy in one of the cases of auricular flutter with audible auricular sounds.[17] However, no evidence of active or adhesive pericarditis was found in Case 1.

SUMMARY

1. Two cases of auricular flutter in which audible auricular sounds were graphically recorded are added to the eight cases already reported.

2. The cases presented were unusual in the following respects:

a. The exceptional loudness of the auricular sounds, which approached or exceeded the ventricular sounds in intensity,

b. The point of maximal intensity in the pulmonic and aortic auscultation points, respectively,

c. The presence of palpable and mechanically recordable impulses synchronous with the auricular sounds and the flutter waves in one case,

d. The intensification of the sounds by the intravenous injection of a digitalis glycoside in the other case,

e. Perfect synchrony with the flutter wave of the electrocardiogram except in the cycle immediately following ventricular systole, where there was a slight but significant delay in the appearance of the sound,

f. The clicking character of the sounds,

g. The occurrence of a loud auricular sound during ventricular systole.

6,720 per cubic millimeter with 53 per cent polymorphonuclears, 40 per cent lymphocytes, 3 per cent monocytes, 2 per cent eosinophiles, 1 per cent band forms, and 1 per cent Türk's cells. The hemoglobin was 114 per cent (Sahli). An erythrocyte count was not done.

On the third day of the illness the blood pressure was 114/72. The temperature was 98.6° F., and it remained normal thereafter. On the seventh day of the illness, the sedimentation rate of the erythrocytes was 20 *mm.* in one hour (Westergren).

An orthodiagram (Fig. 2) fifteen days after the patient was first seen showed a smaller transverse diameter of the heart, with a more nearly straightened left border.

The patient returned to work three weeks after the onset of this attack. He has had no recurrence of discomfort, and his functional capacity has not been impaired.

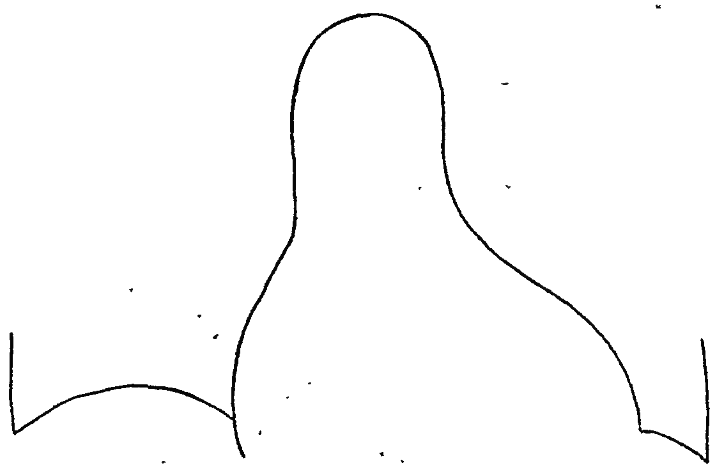

Fig. 1.—Case 1. Description in text.

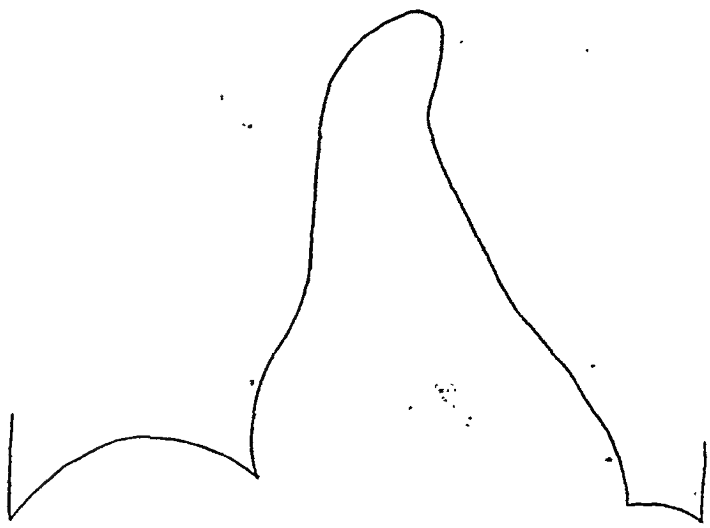

Fig. 2.—Case 1. Description in text.

As will be noted in the series of electrocardiograms (Fig. 3), there was a change from the first apparently normal tracing (T_3 negative) to partial flattening of the T waves in the standard leads, slight inversion of the T wave in precordial Leads $CF_{1, 2, 3 \text{ and } 4}$ and flattening of T in CF_5 two days later. The partial flattening and inversion of the T waves disappeared on the sixth day except in the precordial leads, where the flattening persisted.

The electrocardiogram appeared to be consistent with a diagnosis of pericardial irritation, even though the RS-T segments were not significantly elevated. No abnormal Q waves were present, and there was no reciprocal depression of the S-T segment which is frequently noted in coronary occlusion. Had further studies been made, it is possible that more inversion of the T waves in Leads I and II might have been found.

The changes in the configuration of the heart shadow, as shown by the orthodiagram, offered additional confirmatory evidence.

Case 2.—G. E., a white male truck driver, aged 30 years, gave a history of pain in the midanterior chest, radiating in all directions, and later to the medial surface of the left

ACUTE BENIGN PERICARDITIS

A Report of Two Cases in Young Adults

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Succasunna, N. J.

The frequency with which fatal heart disease has been found in young adults at autopsy makes it imperative that continued efforts be directed toward the early recognition of cardiovascular disease that may be of a benign nature. This is particularly true in this period of universal war, when both the civilian and soldier are being subjected to unusual and prolonged physical strain. Pericardial irritation has long been recognized as of frequent occurrence in rheumatic fever, the earlier stages of acute coronary occlusion, cardiac trauma, and, less frequently, in tuberculosis. Relatively few cases have been reported in which the only preceding incident was a common cold.

Barnes and Burchell[1] recently reported fourteen cases of acute pericarditis of benign, nonsuppurative nature; serial electrocardiographic studies differentiated the condition from acute coronary occlusion. Katz, et al.,[2] and Scott, et al.,[3] in 1929, introduced both experimental and clinical evidence in support of the diagnosis of acute pericarditis by means of the electrocardiogram in animals and man, respectively. Wiggers,[4] in 1930, experimenting with surface application of potassium salts to the pericardium of animals, obtained electrocardiographic changes closely resembling those later noted in cases of proved pericarditis. The largest group of cases (fifty-seven) was reported by Bellet and McMillan,[5] in 1938.

Two additional cases with complete clinical recovery are being reported because of their occurrence in young people, the initial resemblance to acute coronary occlusion, and the changes found in standard and multiple precordial lead electrocardiograms and the orthodiagram.

CASE REPORTS

Case 1.—W. B., a white male powder worker, aged 24 years, gave a history of severe clamping precordial pain of twelve hours' duration, gradual in onset and progressive in severity. When first seen he was pale, with a cyanotic hue to the lips and nail beds, and was dyspneic, orthopneic, and weak, but not perspiring.

The patient stated he had had a slight cold a week previously, but had continued to work. There was no past history of cardiovascular disease in this man or his family. For eight months he had had a recurrent discharge from one of his ears following traumatic rupture of the eardrum.

Physical examination revealed a definite friction rub, best heard in the second and third left intercostal spaces close to the sternum. The heart sounds were of poor quality, with no murmurs or arrhythmias. The lungs were normal throughout. There was slight tenderness in the epigastrium. The liver was not palpable, and the abdomen was otherwise normal. The extremities were not edematous. There was no evidence of peripheral vascular disease. The blood pressure was 120/80.

Further examination by means of the orthodiagram showed slight generalized cardiac enlargement (Fig. 1).

Twenty hours after the acute onset his temperature was 102° F., his pulse rate, 96, and regular, and his blood pressure, 120/80. The friction rub was more pronounced. The following day the temperature was 99.8° F., the pulse rate, 94, the rhythm, regular, and the blood pressure, 100/80. The friction rub had disappeared. The leucocyte count was

Received for publication Sept. 2, 1944.

There were no signs of peripheral vascular disease. The temperature was 98° F., the pulse rate, 80, and the respirations, 36. The blood pressure was 136/78. The sedimentation rate of the erythrocytes was 3 mm. in one hour (Westergren). The leucocyte count was 10,480 per cubic millimeter, with 80 per cent polymorphonuclears, 10 per cent lymphocytes, 4 per cent monocytes, and 6 per cent basophiles. The hemoglobin was 104 per cent (Sahli). The erythrocyte count was 4,790,000 per cubic millimeter.

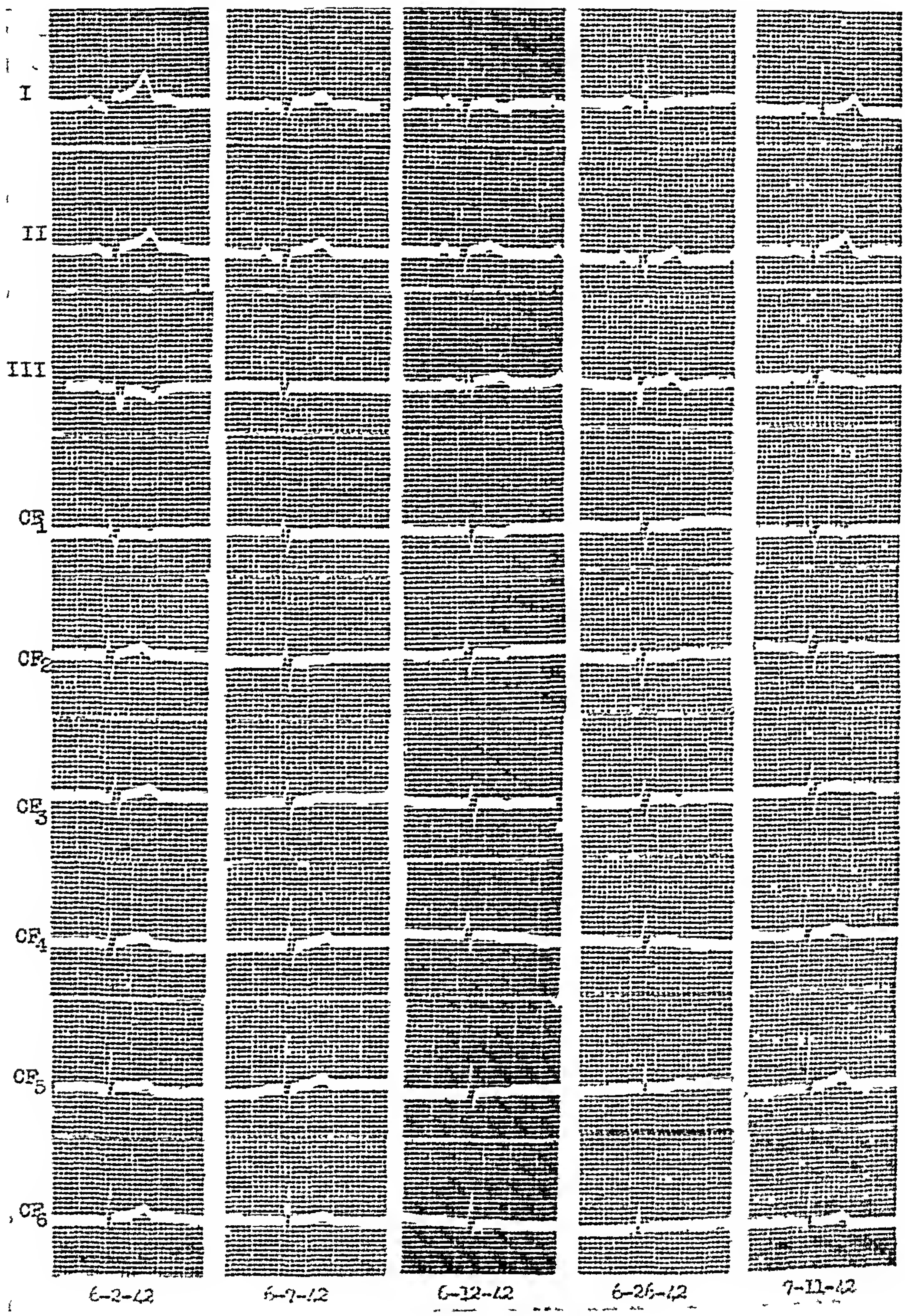

Fig. 4.—Case 2. Description in text.

On the following day the oral temperature was 100° F., the pulse rate, 80, and regular, and the respirations 30. The friction sound was more pronounced, orthopnea was still present, and the pain was described as a soreness in the precordium. On the fourth day his temperature, pulse rate, and respirations were normal; the blood pressure was 110/60, and both the friction rub and pain had subsided. By the eleventh day of the illness the

upper arm to the elbow as an ache. This occurred while driving a truck at night, 300 miles from his home. The pain was accentuated by respiration and movement. He felt weak and perspired. He stopped the truck and slept two hours, during which time the pain subsided, and then he drove home. The pain recurred fourteen hours later and became progressively worse overnight.

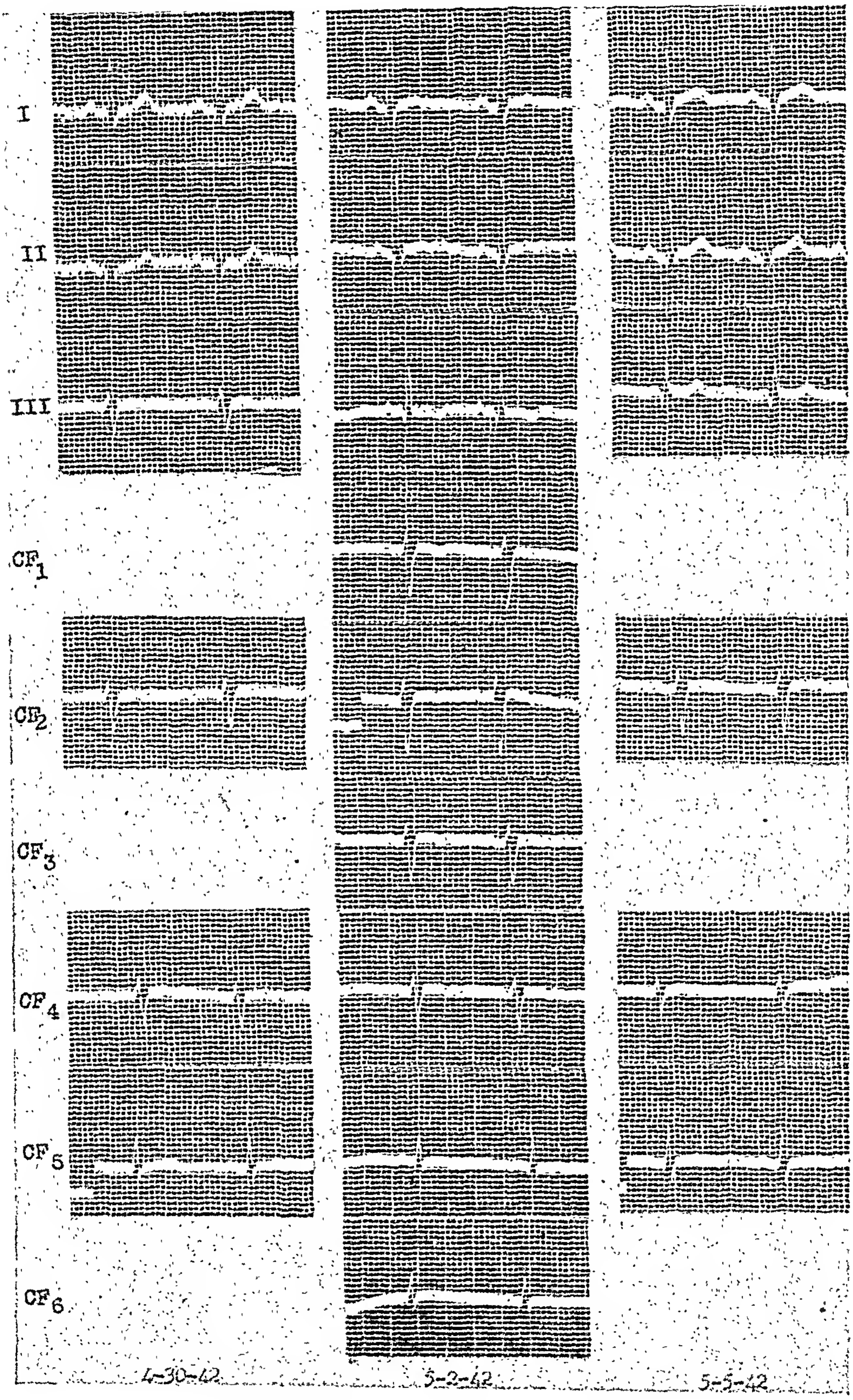

Fig. 3.—Case 1. Description in text.

There was a history of slight nasopharyngitis a week previously. The patient's and his family history were negative for cardiovascular disease.

On physical examination, thirty-three hours after the onset, the patient was orthopneic, pale, and apprehensive. There was a short presystolic scratching friction rub in the lower sternal region. There were no murmurs or arrhythmias, and there was no evidence of cardiac enlargement on percussion. The lungs, abdomen, and extremities were normal.

ELECTROCARDIOGRAPHIC CHANGES IN ACTIVE DUODENAL AND GALL BLADDER DISEASE

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A GROWING literature attests the relationship between upper right abdominal disease and attacks of acute substernal pain which simulate angina pectoris or even coronary occlusion. The subject has been presented recently by Miller[1] and Levy and Boas.[2] An accurate differential diagnosis is essential, especially when surgical risk is involved.

The pain of coronary occlusion is sometimes referred to the abdomen and resembles that of acute upper abdominal disease. In such instances we rely heavily on the electrocardiogram in the differential diagnosis. Our aging population has produced a higher incidence of associated gall bladder and coronary disease, and, rarely, acute conditions in both occur simultaneously.

The following records are of patients who had active gall bladder or duodenal disease; their acute attacks of pain were referred to the substernal region and resembled angina pectoris or coronary occlusion. This type of patient presents a serious problem, and emphasizes the importance of the gastrointestinal tract in cardiology. It is important that the electrocardiographic changes which are found in the presence of these diseases be not misinterpreted. The electrocardiograms of these patients showed an unusual alteration which may be important in the differential diagnosis of acute duodenal or gall bladder disease and coronary occlusion.

CASE REPORTS

CASE 1.—*History.*—This 44-year-old man had experienced vague abdominal distress for many weeks, and had taken soda to relieve upper abdominal and lower chest pressure. His acute illness occurred in April, 1940. While removing his car from the garage after breakfast, he was seized with severe burning pain beneath his sternum which did not radiate, was made worse by movement, and lasted five minutes. He continued with his usual activities during the following few weeks, and had several similar but less severe substernal pains after exertion which were relieved by rest. While performing strenuous activity he had a more severe attack of substernal pain which was accompanied by sweating, mild nausea, and prostration. This attack required morphine, and, during the following night, he was awakened by a most severe attack of substernal pain, with nausea, vomiting, sweating, and the appearance of shock, which again required morphine for relief.

Examination.—He was seen ten hours after his last severe attack of pain, when he was free of symptoms. His pulse rate was 72, and his blood pressure, 100/60. The pupillary and tendon reflexes were normal, and nothing unusual was noted in the lungs. Examination of the heart and blood vessels was negative. Slight, deep, epigastric tenderness was noted. Fluoroscopic examination of the chest a few days later showed nothing abnormal about the lungs or diaphragm, and the heart and aorta were of normal size and shape.

Electrocardiogram.—Fig. 1, *A*, taken May 10, 1940, the day after his most severe attack of substernal pain, shows normal limb leads, but CR_4 shows an isoelectric R-T segment and a positive-negative T wave, the inverted portion being deep and pointed. Fig. 1, *B*, taken June 10, 1940, just prior to ulcer therapy, but after four weeks of rest in bed, shows the same, but less marked, changes in the T waves of Lead CR_4. Fig. 1, *C*, was taken July 2, 1940, after three weeks of treatment for the duodenal ulcer, and is normal in all four leads. Fig. 1, *D*, was taken Nov. 3, 1943. The standard limb leads and chest Leads $CR_{1, 2 \text{ and } 4}$ are normal.

Received for publication Sept. 13, 1944.
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leucocyte count had dropped to 6,760 per cubic millimeter, with 59 per cent polymorphonuclears, 38 per cent lymphocytes, and 3 per cent monocytes. The erythrocyte count was practically unchanged.

Fluoroscopic examination three and one-half weeks after the onset revealed no evidence of pericardial fluid or cardiac enlargement. The patient returned to work, and there has been no recurrence of symptoms.

The electrocardiograms in this case more strikingly correspond to the accepted pattern of acute pericarditis (Fig. 4). Note the early elevation of RS-$T_{1 \text{ and } 2}$ and the inversion of T_3, with the normal precordial series, then the return of RS-T to normal, and the gradual inversion of the T waves in all other leads (except in Lead II, where it became somewhat dome-shaped). These changes appeared first in Lead I and the precordial leads and subsequently disappeared. T_3 changed from negative to positive and then returned to negative. There were no abnormal Q waves and no reciprocal depression of the S-T segment.

SUMMARY

Two cases of acute benign pericarditis of unknown cause are reported, with multiple lead electrocardiographic changes in both, and significant changes in the orthodiagram in one. Both cases occurred in young adults without previous cardiovascular disease. In each case there was a history of a recent upper respiratory infection. The onset in each was suggestive of acute coronary occlusion. The period of disability in Case 1 was twenty-one days, and, in Case 2, twenty-eight days. Both patients returned to full duty. No recurrence of symptoms has been noted to date.

In Case 1 an electrocardiogram eight and one-half months after the acute attack was normal.

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abdominal masses or viscera. The extremities were negative. Fluoroscopic examination of the chest revealed normal heart and aortic shadows and clear lungs.

Electrocardiogram.—An electrocardiogram had been taken in 1934 and reported as normal. Fig. 2, *A*, was taken at his initial examination on April 29, 1940, and shows a flattened T_1, with slight plus-minus inversion; CR_4 has a normal R wave, the R-T segment is isoelectric, and there is a positive-negative T wave, with the inverted portion sharply pointed. Fig. 2, *B*, was taken May 7, 1940, and shows normal limb leads and the changes previously noted still present in CR_4, but with lower T-wave amplitude. On April 29, 1941, Fig. 2, *C*, was taken and is normal; the T wave in CR_4 is now entirely upright and of normal contour and amplitude. His latest curve, Fig. 2, *D*, taken Feb. 3, 1944, includes chest leads CR_{1-6} and is normal.

Treatment and Progress.—He was in the hospital during May, 1940. The gastrointestinal roentgenologic examination revealed "diverticulum of the duodenum, with signs of irritability." After several weeks of rest and dietary and medical treatment, the symptoms disappeared except for slight distress in the lower sternal region on exertion. On Feb. 3, 1944, he was free of all symptoms and was carrying on his regular work, but he was still following dietary restrictions.

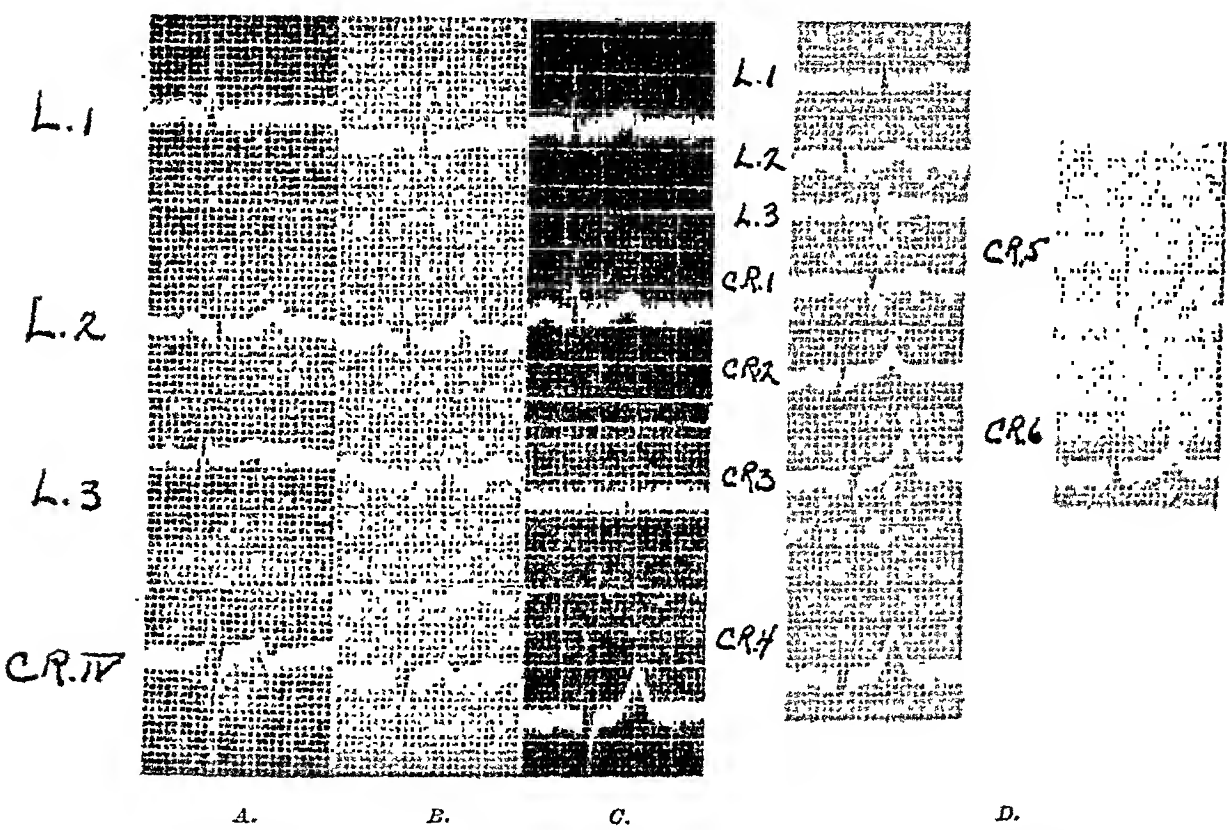

Fig. 2.—*Diagnosis:* acute duodenal diverticulitis. *A*, taken April 29, 1940, twenty-four hours after attack of severe substernal pain, shows that the T wave in Lead CR_4 is plus-minus diphasic. *B* was taken May 7, 1940, eighteen hours after severe attack of substernal pain; the T wave in Lead CR_4 is still diphasic, but of decreased amplitude. *C* was taken April 29, 1941, after dietary and medical treatment, and is normal. *D*, taken Feb. 3, 1944, is normal in all four leads.

CASE 3.—*History.*—A physician, 57 years of age, had attacks of substernal, squeezing distress which occurred with or without exertion and had been present over a period of twelve years. These pains were associated with definite abdominal distress, bloating, and belching. Of late years the substernal, squeezing pain had been accompanied by an ache in both arms. Certain foods, as well as exertion, would precipitate an attack, and rest or a sedative would usually bring relief. He had had an attack of acute cholecystitis twenty-five years before, and ten years before was told that he had coronary occlusion and would not live six months. In August, 1941, while walking, he suffered his most severe attack of constricting substernal pain which did not radiate, and was associated with marked gastric distress. Standing still gave relief, but he was able to walk several blocks to his home. He perspired profusely, vomited, and required morphine; he was in a state of mild shock. He felt perfectly well the next morning, and his later recovery was rapid and uneventful.

Treatment and Progress.—He was hospitalized in May, 1940, after his last severe attack of substernal pain, and a few weeks later a gastrointestinal roentgenologic examination revealed: "Chronic duodenal ulcer, with associated irritability and spasm suggesting activity at this time." He was placed on ulcer therapy June 11, 1940. On July 2, 1940, he was free from all symptoms, but in December, 1940, he noted a slight burning pain in the lower part of the right hemithorax, radiating up to the substernal region, which occurred following exertion after meals. On Nov. 3, 1943, he was free of symptoms. He had been working very hard since December, 1940, without dietary restrictions, and there had been no recurrence of the chest pains or any other symptoms. The upper gastrointestinal roentgenologic examination, made Nov. 4, 1943, showed "slight deformity of duodenal bulb, but no evidence of activity."

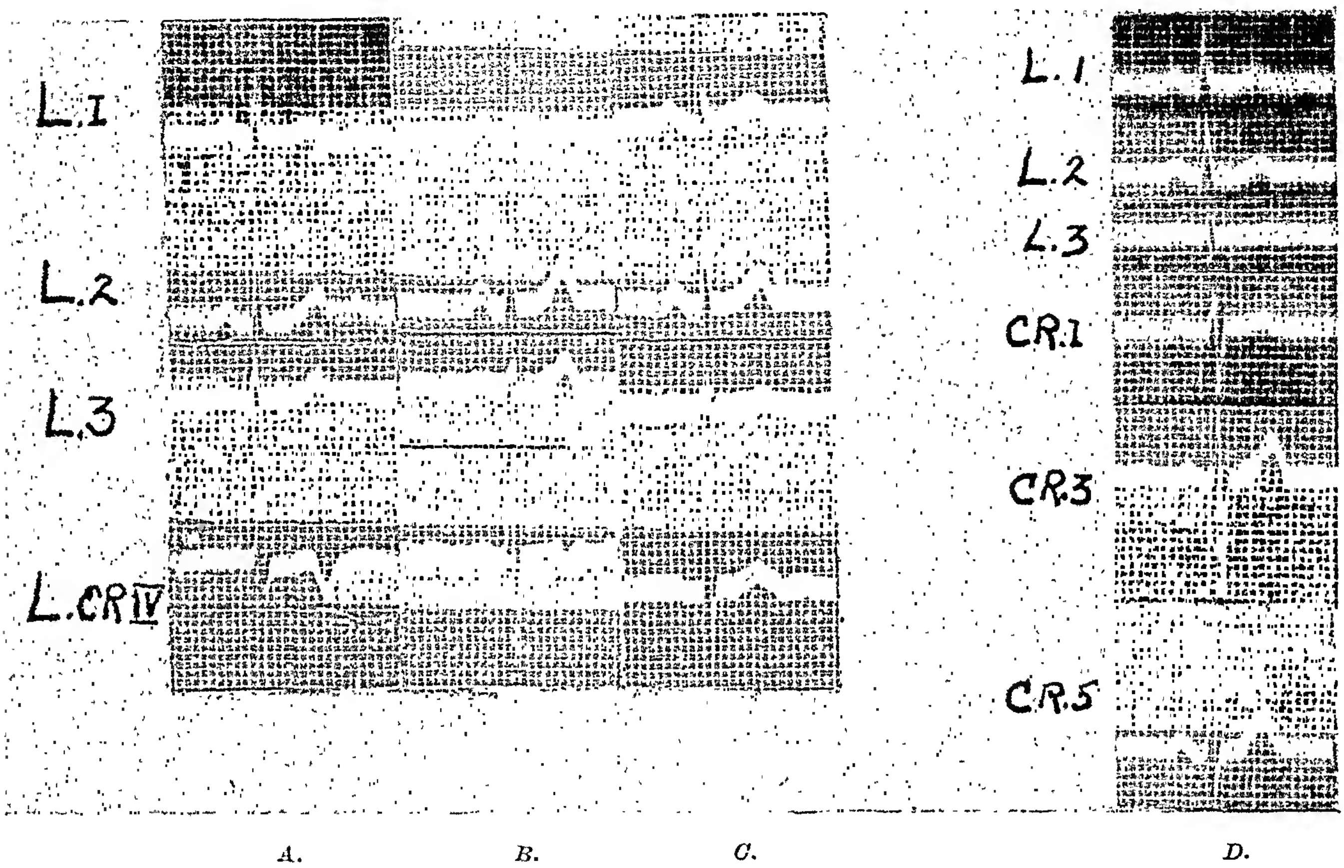

Fig. 1.—Diagnosis: acute duodenal ulcer. *A* was taken May 10, 1940, after an acute attack of chest pain; the limb leads are normal, and the T wave in CR_4 is plus-minus diphasic. *B*, was taken June 10, 1940, just prior to starting ulcer therapy, but, after four weeks of rest in bed, the diphasic T wave in Lead CR_4 was less pronounced. *C* was taken July 2, 1940, after three weeks of ulcer therapy, and all leads are normal. *D*, taken Nov. 3, 1943, includes chest Leads $C_{1-3 \text{ and } 5}$, and is entirely normal.

CASE 2.—*History.*—This 47-year-old man had had "stomach trouble" for thirty years. Eating certain foods would cause flatulence, hyperacidity, and vague abdominal distress. A gastrointestinal roentgenologic examination, done in 1936, showed "mild spasm of the pylorus, with a few retained flecks of barium in the first portion of the duodenum, but no filling defect." Appendectomy was performed at that time, and his abdominal symptoms were relieved until March, 1940. During a long walk he suddenly had severe pain which was squeezing in the precordial and lower sternal regions and radiated into the left arm. Standing still gave some relief, and he was able to continue on to his home. On the following days he had similar pains which were less severe. While at rest in bed he had a very severe attack of pain in the chest which radiated into both arms, and the left arm continued to ache for several hours. There was no nausea or vomiting, but he sweat profusely and was dyspneic. The succeeding night he was awakened by a similar severe pain which spread over the entire anterior portion of the chest.

Examination.—He was seen a few days after his last severe attack of pain, when he was free of symptoms. His resting pulse rate was 72, and his blood pressure was 130/90. The pupillary and tendon reflexes were normal, and examination of the fundi was negative. Both lungs were normal, and the heart was of normal size; its rhythm was regular, and the sounds were good, with no murmurs and normal accentuations at the base. There was slight tenderness deep in the epigastrium, but no muscle spasm, and there were no palpable

Acute inflammatory and ulcerative conditions involving the gall bladder or duodenum cause irritation and spasticity of surrounding structures and create stimuli which act reflexly through autonomic pathways[1] to restrict or in some other manner alter the coronary blood supply, so that existing minor deficiencies in the coronary circulation become manifest. It seems probable that people with acute duodenal or gall bladder disease whose electrocardiograms show the transient changes I have described do have minor alterations in their coronary circulation; otherwise, all people with such acute conditions would show similar electrocardiographic patterns.

These cases are presented not to deny the presence of coronary artery disease, but to show that acute upper abdominal disease can prematurely reveal subclinical changes in the coronary circulation. This characteristic pattern in the electrocardiogram should not be interpreted as indicating coronary occlusion. Others have observed the relationship between the gastrointestinal tract or gall bladder and cardiac symptoms.[1-7]

In Case 3, with acute gall bladder disease, the existing changes in the coronary circulation or the reflex stimulus may have been greater or of longer duration than in the others, and, accordingly, the temporary change in the electrocardiographic pattern involved not only the chest lead, but the limb leads as well. However, if there was any disease of the coronary arteries or a diminished coronary circulation, it was still below a clinically diagnosable level, and was revealed by an upper abdominal disease crisis. The alterations in the electrocardiogram were caused by temporary myocardial ischemia and in all instances disappeared.

It is debatable whether chronic or acute gall bladder disease is harmful to the heart. I believe that these cases show that it can be an aggravating factor in heart disease. The repeated crises of the abdominal disease, with temporary embarrassment of a possibly, although slightly, altered coronary circulation, certainly influence the future welfare of that heart. These records suggest a diagnostic change in the electrocardiogram, and point out the desirability of prompt corrective measures to safeguard such patients against repeated disturbance of their coronary circulation.

CONCLUSIONS

1. Three instances of syndromes like coronary occlusion which were induced by acute upper abdominal disease are reported.

2. A constant, but not persistent, change was noted in the T waves of the electrocardiograms.

3. The relationship of upper abdominal disease and heart symptoms is discussed.

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Examination.—He was first examined in March, 1941, during an attack of substernal pain. He was pale and emotionally disturbed, the pupillary and tendon reflexes were normal, the teeth were in poor condition, the heart rate was 48, and the blood pressure was 125/80. The lungs were normal, and the heart was of normal size; its rate was slow, the sounds were good, the accentuations at the base were normal, and there were no murmurs. There was distinct tenderness in the upper right quadrant of the abdomen, but no palpable masses or viscera, and the extremities were negative. During his acute attack in August, 1941, the blood pressure was elevated to 160/74, while the pulse rate remained at 48. His leucocyte count was 14,000, with a normal differential count, and the count dropped to 7,600 within thirty-six hours. There was no rise in temperature. Several weeks after this acute attack, cholecystograms were reported as showing evidence of chronic cholecystitis.

Electrocardiogram.—His first electrocardiogram, Fig. 3, *A*, was taken May 9, 1940, and shows bradycardia and slight elevation of the R-T segment in Lead I and a normal CR_4. Fig. 3, *B*, was taken twelve hours after his severe attack of substernal pain in August, 1941, and shows slight elevation of the R-T segment in Lead I, depression of the same segment in Lead III, a plus-minus T wave in Lead I, and a minus-plus T wave in Lead III. The T wave in CR_4 shows the same plus-minus change. Fig. 3, *C*, taken three days later, on Aug. 13, 1941, shows similar, but less marked, changes in the T waves of Leads I, III, and CR_4. Fig. 3, *D*, was taken Nov. 23, 1943, and reveals normal limb leads and a normal CR_4; the amplitude of the R wave has returned to its former normal, and the T wave is upright.

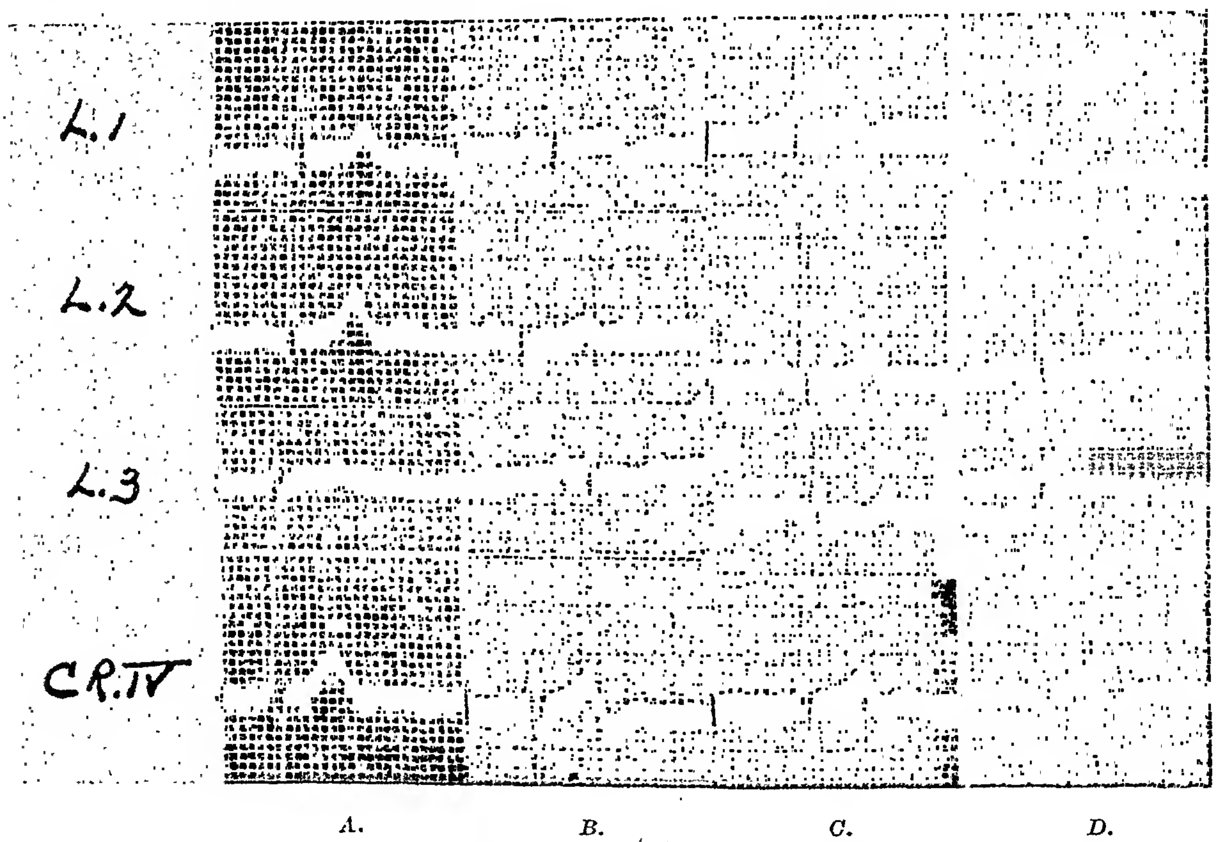

Fig. 3.—Diagnosis: acute cholecystitis. *A* was taken May 9, 1940, and shows bradycardia, but otherwise is normal. *B* was taken Aug. 9, 1941, twelve hours after attack of severe substernal pain; the R-T segment is elevated in Lead I and depressed in Lead III; T_1 shows plus-minus, and T_3, minus-plus inversion; in CR_4 the R-T segment is isoelectric and the T wave shows a plus-minus inversion. *C* was taken Aug. 13, 1941, and shows bradycardia and similar, but less pronounced, changes in the T waves of Leads I, III, and CR_4. *D*, taken Nov. 23, 1943, is normal; the R wave in CR_4 which was decreased in the electrocardiogram of Sept. 25, 1941, has assumed its former amplitude.

DISCUSSION

There are many conditions which temporarily alter the electrocardiogram. Recently, Scherf, et al.,[3] have discussed electrocardiographic changes which they attribute to acute hemorrhage from duodenal ulcers. However, they observed that the electrocardiographic changes were not altered by transfusions, nor did they bear any relationship to the hemoglobin content of the patients' blood.

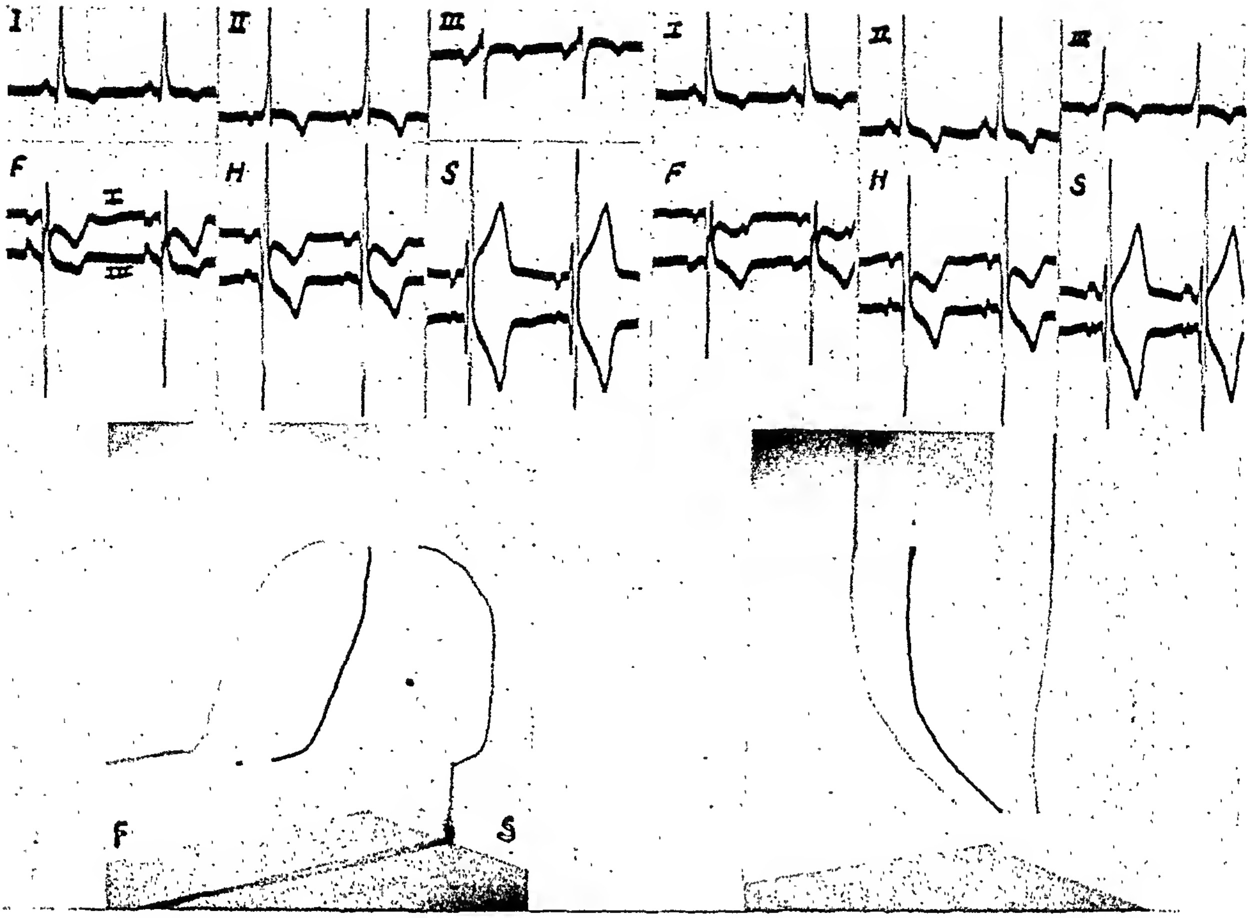

Fig. 1.—A-V nodal rhythm; sinus rhythm. In each of the figures the conventional limb leads are shown on the upper line. Below are the simultaneously recorded Leads I and III in the frontal (F), horizontal (H), and sagittal (S) planes, placed in that order from left to right. In the photograph below the electrocardiograms, the black wire represents the direction of movement of the atrial electrical axes for consecutive intervals of 0.01 second. The shadows cast by the wire reproduce the graphs obtained for the frontal and sagittal planes.

In Fig. 1, the group at the left represents the consecutive atrial axes during A-V nodal rhythm; that on the right represents sinus rhythm in the same patient.

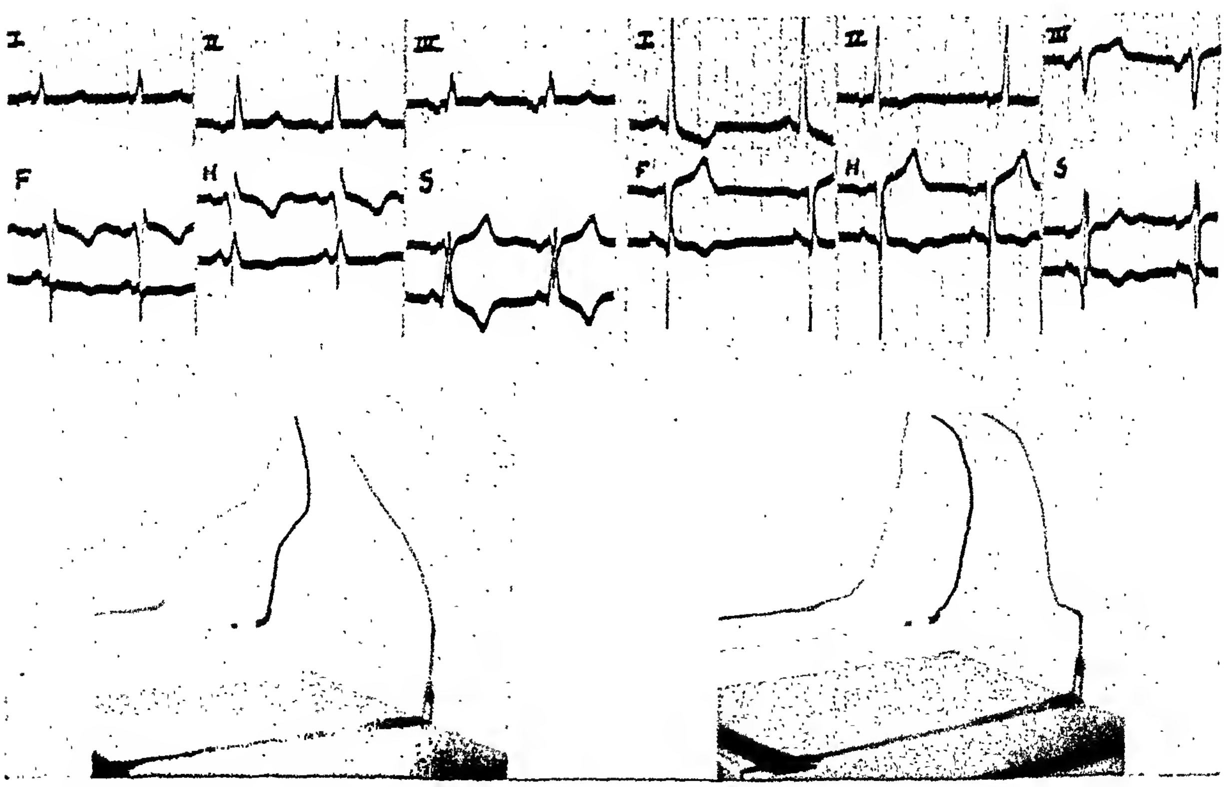

Fig. 2.—The direction of the consecutive atrial electrical axes in two additional cases of A-V nodal rhythm.

MOMENTARY ATRIAL ELECTRICAL AXES

III. A-V Nodal Rhythm

Arthur Ruskin, M.D., and George Decherd, M.D.
Galveston, Texas

We have previously described the patterns obtained by graphing in three dimensions the consecutive momentary atrial electrical axes in sinus rhythm[1] and in atrial flutter, atrial fibrillation, and paroxysmal tachycardia.[2] Using the same methods we have obtained similar data from patients with A-V nodal rhythm.

Typical A-V nodal rhythm is characterized in man by the presence of negative P waves in Leads II and III of the electrocardiogram. Since the early experiments of Ganter and Zahn[3, 4] and Meek and Eyster,[5] the position of the P wave in relation to the QRS complex has been taken to indicate the position of the nodal pacemaker in the upper, middle, or lower portions of the A-V node, with atrial excitation occurring before, with, or after ventricular excitation, respectively. Scherf[6] conceived that a change in the position of the pacemaker was not essential to variation in the relation of the P wave to the QRS complex, but that delay in infranodal conduction might cause a positive P-R interval in cases in which atrial and ventricular complexes would otherwise have been superimposed. Rothberger and Scherf[7] found that the speed of retrograde conduction from the node to the atria might affect the relative position of the P and QRS complexes in experimental animals. Recently, Langendorf, Simon, and Katz[8] have cited clinical examples which suggest that the relative speeds of retrograde and antegrade conduction from a single nodal pacemaker may explain the variable positions of the atrial and ventricular complexes.

A distinct variety of nodal rhythm is that in which the P waves are upright in all leads, with a P-R interval of 0.12 second or less. This is often referred to as a "coronary" nodal rhythm, and the pacemaker is assumed to reside in those ramifications of the A-V node which adjoin the coronary sinus. The statement that at least 0.12 second is consumed in the passage of the impulse through the nodal tissue to the ventricles implies as a corollary that the pacemaker must be within the node whenever the P-R interval is equal to, or less than, that figure. Other alternative interpretations will be discussed later. This type of nodal rhythm is not uncommon clinically.

On the other hand, A-V nodal rhythm with negative P waves in Leads II and III is rare, and often transient. We have been able to study five examples of this mechanism by means of chest leads so placed that the Einthoven triangles which were formed lay in the frontal, horizontal, and sagittal planes.[1] Our earlier experience with this method led us to the conclusion that the curves and three-dimensional models constructed from such electrocardiographic data might be modified by changes in the site of the pacemaker, in the position of the heart, or by the quality of the myocardium as a conducting medium. In this paper we are concerned chiefly with the demonstration of the sequence of atrial excitation when the pacemaker of the heart is in the A-V node, as reflected in the sequence of changes of the mean atrial electrical axes.

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Received for publication Sept. 13, 1944.

anticipated that the P of Lead I would have been negative in this case, but it is virtually isoelectric.

"Coronary" Nodal Rhythm.—In Fig. 4 we have shown the electrocardiograms, and models constructed from them, derived from two patients with the so-called "coronary" type of nodal rhythm. In these instances the P-R interval is 0.10 and 0.11 second, respectively. The curves in these cases differ in no way from those obtained from patients with sinus rhythm; both curves point down, forward, and to the left. This indicates that the spread of excitation over the atria is similar in "coronary" nodal rhythm to the spread in sinus rhythm, insofar as this may be deduced from the consecutive electrical axes. It also suggests that the site of the pacemaker, or rather the point at which the impulse enters the atria, is very little different in the two types of rhythm, if, indeed, there is any difference at all. The question logically arises as to whether or not this variety is genuine nodal rhythm, with the pacemaker within the A-V node. This question has been raised before, and will be elaborated upon.

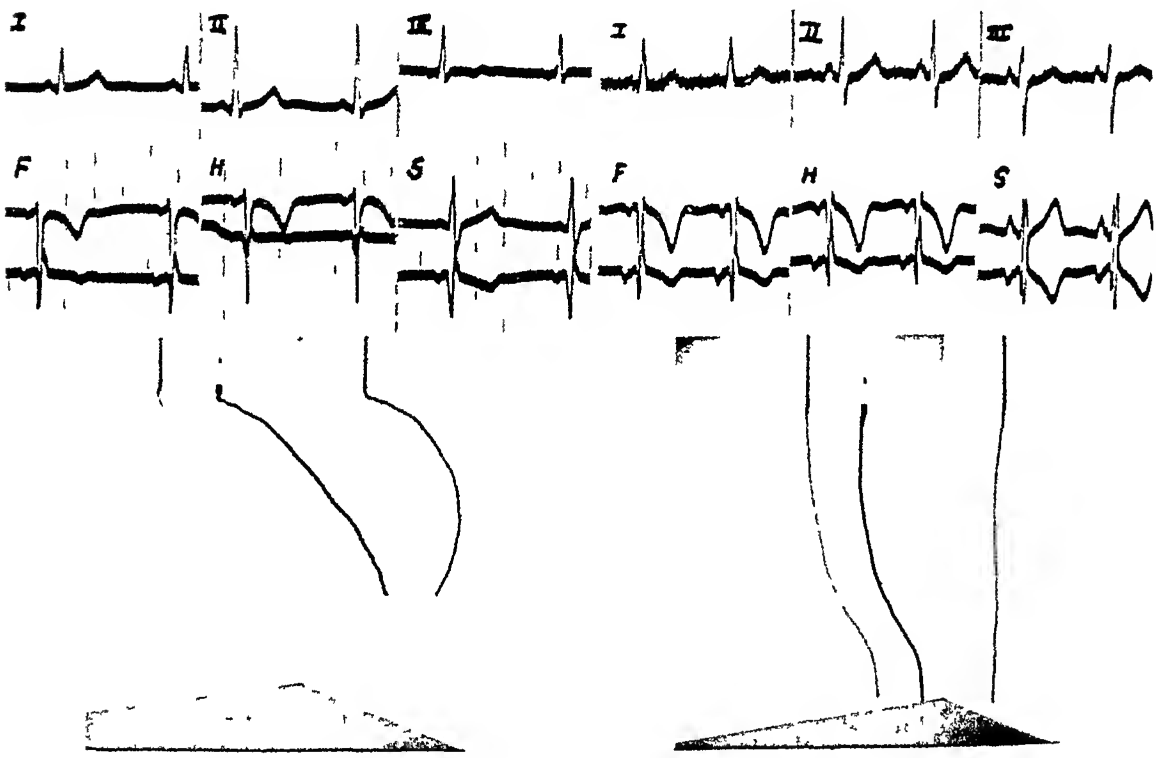

Fig. 4.—Two examples of "coronary" nodal rhythm, see text.

DISCUSSION

Atrioventricular nodal rhythm was first described by Engelmann,[10] who observed almost simultaneous atrial and ventricular contraction after exclusion of the S-A node by the first Stannius ligature; he assumed that under these circumstances the pacemaker of the heart was on the ventricular side of the A-V ring. Lohmann[11] corroborated these conclusions in the mammalian heart. He also confirmed the Stannius-Munk phenomenon—the production of nodal rhythm by needling the A-V nodal region (Brückenfäsern).

Zahn and his associates[3, 4] later attempted to localize the seat of impulse formation more exactly within the A-V nodal tissue, and showed that the atrial rate was affected by cooling the upper part of the A-V node near the coronary sinus in those cases in which atrial preceded ventricular contraction. When atrial and ventricular contractions were simultaneous, the middle portion of the node appeared to control impulse formation, and when atrial followed ventricu-

EXPERIMENTAL RESULTS

Cases in Which There Were Negative P Waves in Leads II and III.—Fig. 1 contrasts the curve of the momentary axes when the pacemaker is in the A-V node with that obtained when the impulse originates in the S-A node. In normal hearts with sinus rhythm the curves usually run smoothly down, variably forward, and to the left.[1] In this case the curve during sinus rhythm is not clearly abnormal, and, although it deviates slightly from the average in running down, slightly backwards, and to the left, this is within the normal range of variation. When the pacemaker is within the A-V node, however, the curve is strikingly changed, passing up, backwards, and to the left. Two additional instances of A-V nodal rhythm are illustrated in Fig. 2, in both of which the curves are similar to that of Fig. 1, i.e., are directed up, back, and to the left.

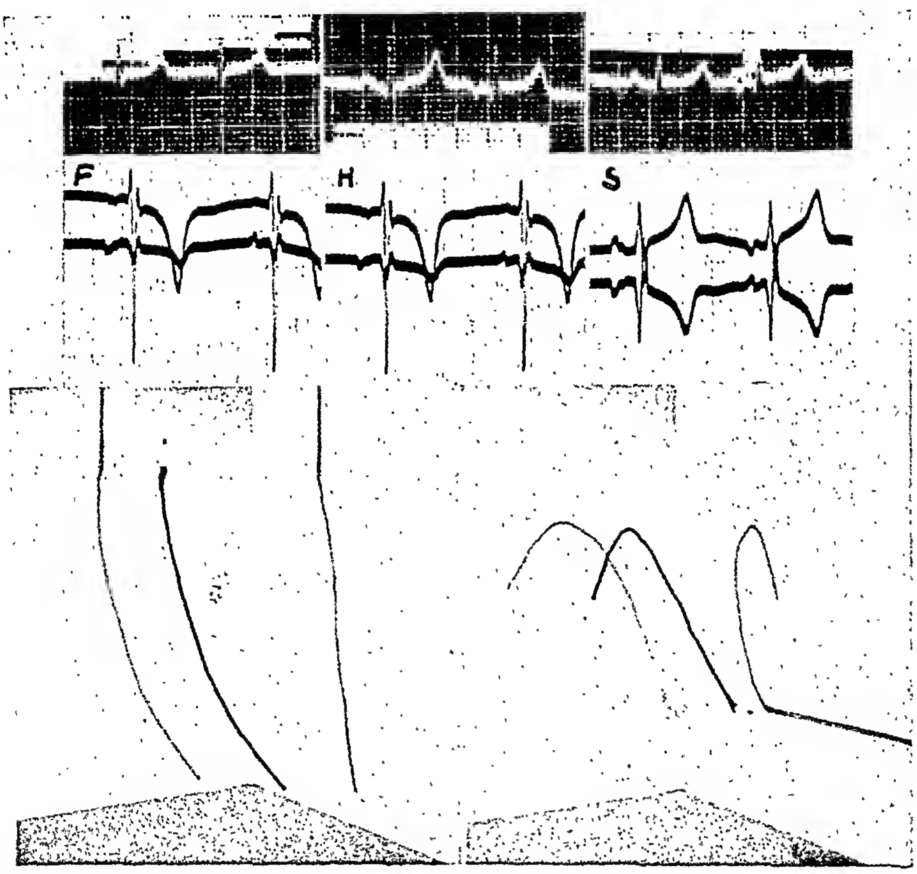

Fig. 3.—Sinus beat; atrial premature beat. Electrocardiograms and models of a sinus beat, followed by a premature beat of atrial origin.

Fig. 3 illustrates the data obtained from a patient who had premature beats which we, at first glance, thought might arise in the A-V node, inasmuch as the P waves of the premature beats were negative in Leads II and III. Analysis of the electrocardiograms obtained in the three planes, with construction of the three-dimensional model shown, indicates that the mean electrical axes pass, from moment to moment, up and to the right, and later pass down, forward, and to the right. The sinus beats gave a normal curve. This indicates to us that the premature beats probably arose in an ectopic focus located in the lower part of the left atrium. These observations also indicate that negative P waves in Leads II and III do not necessarily place the pacemaker in the A-V node. Whenever the ectopic focus is in such a position that the spread of excitation is cephalad, as in the atrial premature beat analyzed by Schellong[9] with special frontal plane leads, the projection of the mean electrical axis on Leads II and III will be such that the P waves in these leads will be negative. We would have

in the limb leads that the results would not differ from those in cases in which P waves precede the QRS. We feel justified in assuming that, whether the pacemaker shifts in the A-V node, or, as seems more likely, the speed of retrograde conduction is the chief variable, the retrograde pathway is usually so situated that the impulse enters the atria at such a point that the spread of excitation, as judged by the directions of the consecutive mean electrical axes, is up, back, and to the left. The fact that variable retrograde pathways have been postulated[14, 16] does not invalidate this generalization.

The term "coronary" nodal rhythm was first employed by Edens;[17] since his studies were all on venous pulse tracings, it is doubtful whether he used it in the sense in which it is now understood, viz., upright P waves in all three limb leads, with a P-R interval of 0.12 second or less.[18] Clerc and Pezzi[19] described a supraseptal rhythm, but again all of the records were mechanical. Meek and Eyster[5] found initial negativity in one of two places, usually in the ventricular portion of the A-V node or near the coronary sinus, in escaped beats during vagus stimulation in the dog, but here again there was no correlation with the form of the P waves in the limb leads.

At present the term is employed for tracings with upright P waves in all leads, but with a P-R interval of 0.12 second or less. Absence of the typical pattern of retrograde conduction, i.e., negative P waves in Leads II and III, has necessitated many hypothetical attempts at explanation. Assuming that the pacemaker in such cases actually lies in the A-V node, the upright P waves might be explained as a result of (1) intra-atrial block, producing a pathway similar to that of sinus beats; (2) a variable retrograde pathway through a ramification of the A-V node near the coronary sinus or the S-A node, and different from the one traversed by impulses giving the usual negative P waves in Leads II and III; or (3) location of the pacemaker in fibers of the A-V node near, or to the right of,[8] the coronary sinus (hence "coronary" nodal rhythm). On the other hand, if the pacemaker in these cases is supranodal, it might lie in (1) islands of S-A nodal tissue[20] or ramifications of the S-A node in the neighborhood of the coronary sinus; (2) in the tail of the S-A node, nearer the A-V node than normal; or (3) in the usual position in the S-A node, but with unusually rapid conduction (a) from the S-A to the A-V node, possibly through special functional pathways, or (b) through the A-V node.

Rothberger and Scherf[7] and Condorelli[21] found that negative P waves could be associated with sinus rhythm, and, conversely, that positive P waves might be seen in A-V nodal rhythm, facts which they explained as the result of variable intra-atrial conduction. The usual retrograde pathway from the A-V nodal pacemaker enters the atrium at a point which gives the type of curve shown in Fig. 2. We have described variation in the retrograde pathway which is sufficient to give alternation of the P waves.[14] It is conceivable that the impulse traverses those fibers which lie near the coronary sinus, and, in effect, enters the atrium in the same fashion as it would have, had the impulse actually originated in the fibers of the A-V node near, or to the right of, the coronary sinus.

Holzmann and Scherf[20] had a single animal whose S-A node had been cut away, in which they were able to produce positive P waves, just preceding the QRS complexes, by warming the mouth of the coronary sinus. This same animal later yielded negative P waves, as did their other animals. They were inclined to regard these exceptional results as being due to the presence of isolated islands of S-A nodal tissue in the vicinity of the mouth of the coronary sinus.

lar contraction, the pacemaker was thought to be in the ventricular portion of the node. These experiments form the basis for the concept of upper, middle, and lower nodal rhythm. In experimental nodal rhythm, Meek and Eyster[5] found initial negativity either in the region of the coronary sinus or in the ventricular portion of the A-V node, and interpreted their results as confirming those of Zahn. Neither group of workers correlated their observations with the limb-lead P-wave patterns.

Both Lewis[12] and Scherf[13] pointed out the uncertainty of localization of portions of a small, deep-seated structure such as the A-V node. Scherf[6, 13] also critically surveyed Zahn's experimental technique, and cast doubt upon the latter's concept by failing to confirm his experimental results. Scherf found that the various experimental procedures which are calculated to produce A-V nodal rhythm almost invariably produced the so-called middle variety, the type also most commonly seen in patients. For example, he found that, after resection of the S-A node in the dog more completely than had been accomplished by Zahn, the P and QRS complexes were superimposed in ten experiments, there was a short P-R interval in two, and a negative P-R, or R-P, interval in two others. Further warming of the higher portions of the A-V node failed to accelerate the rate, or to produce a positive P-R interval when superimposition or an R-P interval was present. In fact, in the two cases in which there was a short, positive P-R interval, warming of the upper portion of the A-V node caused the P wave to merge with the QRS. Scherf concluded that conduction is slower to the atrium (retrograde) than to the ventricle, thus explaining the shortening of the P-R interval. Langendorf, Simon, and Katz[8] have elaborated this concept to explain all three types of nodal rhythm as the result of variation in the relative speeds of conduction from the nodal pacemaker to the atria and ventricles. Our own[14] studies of varying rates of retrograde conduction, both spontaneous and under drug influences, would lead us to concur in the idea that variable retrograde conduction determined the position of the P wave in relation to the QRS complex. Retrograde conduction was, we found, more markedly affected by drugs than was forward conduction, although, of course, changes in the latter might readily play a role in determining the position of the P wave.

Quite recently, Scherf,[15] in pursuit of his earlier efforts to produce A-V nodal rhythm by stimulation of the coronary sinus branches of the node, reported that warming the coronary sinus on the epicardial surface produced nodal tachycardia, with negative P waves preceding the QRS in Lead II. This occurred even though the same stimulus had failed to produce negative P waves preceding the QRS, when applied to the endocardial surface. The P-R intervals were not short, but were equal to, or longer than, the P-R intervals during sinus rhythm. This is referred to as an "upper auriculoventricular rhythm (coronary sinus rhythm)," and is not comparable to the "coronary" nodal rhythm with upright P waves described below. We have pointed out above that the P waves may be negative in Leads II and III whenever the impulse spreads in a cephalad direction, e.g., the case illustrated in Fig. 3. It is to be anticipated that any impulse arising near the A-V ring would spread in this fashion. We have found that in human A-V nodal rhythm the direction of the impulse is cephalad, and also back and to the left. It remains to be proved that the impulse from the point stimulated by Scherf will spread in this fashion; we would expect it to spread forward rather than backward.

Middle nodal rhythm would not, of course, be susceptible to analysis by our method, for no P waves are visible. We have had no case with retrograde P waves available for study, but are confident from the contours of the P waves

QRS complexes. The latter authors accept such P-R intervals as indicating unusually rapid conduction from atria to ventricles, with less than the usual delay in the A-V junctional tissues.

It may be of interest, in passing, that the consecutive electrical axis pattern of the P wave in the short P-R, long QRS syndrome is of the usual S-A nodal type in the single case we have analyzed. Pezzi[25] considered this type of curve as an example of a supraseptal rhythm.

We believe that the evidence cited proves that the so-called "coronary" type of nodal rhythm is not a variety of A-V nodal rhythm, but is, in fact, simply normal sinus rhythm with a short P-R interval, which, in accordance with the laws of distribution, occurs relatively uncommonly.

SUMMARY

Using a method of analysis of the P wave, recorded in three planes of the chest as previously described, we have studied the curves of the consecutive momentary atrial axes in A-V nodal rhythm. In three dimensions, the curves pass up, back, and to the left.

The curves obtained in so-called "coronary" nodal rhythm resemble those of ordinary sinus rhythm, passing down, variably forward, and to the left. The available evidence is surveyed, and it is concluded that this latter type of nodal rhythm is actually merely an example of sinus rhythm with relatively rapid conduction of the impulse through the A-V junctional tissues.

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Our data, as depicted in Fig. 4, indicate that the spread of excitation over the atria in "coronary" nodal rhythm is indistinguishable from that in normal sinus rhythm. We infer from this that the impulse enters the atria in approximately the same place in both conditions. The normal, smooth contours of the curves fail to provide any evidence for the presence of a conduction defect with intra-atrial block, and indicate that such a disturbance of conduction is not the cause of the upright P waves. Nor do they support the view favored by Langendorf, et al.,[8] that upright P waves with short P-R intervals arise from proximal fibers of the A-V node, lying to the right of the coronary sinus. We are accustomed to thinking of the upper fibers of the A-V node as being closely related functionally to the S-A node, with the pacemaker moving to the former when the latter is depressed. Although experimental proof of such a concept is far from convincing, of more importance to us at the moment is the fact that anatomically these two areas are well removed from each other. We would anticipate that impulses arising from the neighborhood of the coronary sinus would spread quite differently from those springing from the S-A node, and would yield entirely different patterns when the consecutive atrial electrical axes were graphed. Of course, experimental evidence would be necessary to prove the truth of this conjecture, but it receives some support from Scherf's recent paper.[15]

Lewis felt that the excitation wave spread concentrically from the S-A node throughout the atrial muscle, stimulating the A-V node in passage. There is some evidence, however, of specialized functional pathways within the atrial musculature. Meek and Eyster, Rothberger and Scherf, and Condorelli found evidence of a special connection between the two nodes; these pathways were not demonstrable anatomically, but were considered to be functional pathways. These claims might give substance to the possibility that shortening of the P-R interval below 0.12 second in sinus rhythm might be due to acceleration of conduction along such a pathway. Consideration of the fact[12] that only about one-third or one-fourth of the P-R interval is required for excitation of all the atrial muscle, and that presumably much less than this is occupied in passage of the impulse to the A-V node makes it seem unlikely that any appreciable shortening of the P-R interval could be due to acceleration of intra-atrial conduction.

It is well established that the major delay in atrioventricular conduction occurs in the A-V nodal tissue.[12] The length of time usually required for passage of the A-V junction is probably more than one-half of the P-R interval; more rapid conduction at this point could well decrease the P-R interval to below 0.12 second. These A-V junctional tissues are known to be most susceptible to humoral and nervous influences which affect conduction.

It is not warranted to place a lower limit of 0.12 second on the normal P-R interval, as has been done by many authors, including Scherf and Schönbrunner.[22] Recent studies have shown that among large groups of apparently normal persons the A-V conduction times follow a fairly symmetrical distribution curve. Stewart and Manning[23] have reported an analysis of the electrocardiograms of five hundred Air Corps personnel. They found that the mean P-R interval in Lead II was 0.16 ± 0.001 second; the limits of twice the standard deviation on each side of the mean were from 0.11 to 0.21 second, and, of three times the standard deviation, 0.09 to 0.24 second. Graybiel, et al.,[24] in a similar study of one thousand healthy aviators, found a mean P-R interval in Lead II of 0.154 second; this excluded two examples of short P-R interval with prolonged

The patient's recovery was excellent, and he had been feeling fine, when, suddenly, on the sixteenth day after the attack described, he felt uncomfortable and complained of pain in the lower part of the abdomen. The following night he was unable to sleep, felt very restless, and complained of severe pains in the abdomen and testicles When I saw him the next morning, the left testicle, previously normal in size, had swollen to the size of a large orange; it was very sensitive and painful, and the scrotal skin appeared tense and red. The temperature was normal (98°), and the abdomen somewhat tender, with no rigidity of the abdominal walls. That evening the temperature was 98.6°; no higher temperature was found in the following days. The pulse rate, which had ranged between 76 and 80 in the previous days, had risen to 96; the blood pressure was 135/80. There was no swelling of the parotid gland, nor was there any history of exposure, in the weeks previous, to the mumps. A modified suspensory was applied and cool compresses recommended. The following day the pulse rate was 90, and the day after that, 84. In the course of a week the pain gradually was relieved and the size of the testicle reduced, but the hydrocele remained quite obvious and identifiable as a light-translucent swelling of the left testicle alone. During the next three weeks the testicle shrank to about half the size it had displayed on the occasion when it had swelled and caused so much pain; nevertheless, it remained definitely and abnormally enlarged as compared with the normal one. In the meantime, the heart condition had improved so well that, after the sixth week, the patient was able to stay out of bed and later felt sufficiently comfortable to return to his normal occupation as a research worker.

The most satisfactory explanation for this series of events seems to be as follows. A small mural thrombus due to coronary occlusion gave rise to an embolism which produced the symptoms described. As is well known, emboli in other parts of the body are not rare occurrences after cardiac infarction.

SUMMARY

This case is unique in that, on the sixteenth day after indubitable cardiac infarction, orchitis and hydrocele developed in conjunction with intense abdominal pain. The explanation offered for this picture is embolism due to mural thrombi caused by cardiac infarction.

SILICOSIS OF THE PERICARDIUM

Case Report

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RECENTLY we[1] completed a study of sixty-four cases of silicosis and silicotuberculosis. In a few of these, silicotic foci were found in the spleen and liver, apparently as a result of hematogenous dissemination of siliceous particles. However, in the majority, the silicotic foci were limited to the lungs and draining lymph nodes, and in no case was there evidence of lymphatic dissemination to any other organ of the body. Since the completion of this study,

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Received for publication Dec. 17, 1943.

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Clinical Reports

ORCHITIS AND HYDROCELE AFTER CARDIAC INFARCTION

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THE following case seems worth reporting because no similar observation has been reported.

CASE REPORT

The patient was a white man, 64 years of age. There was no previous history of illness and no history of venereal disease. In August, 1941, when the patient came under my observation, he showed definite signs leading to a diagnosis of coronary sclerosis. At that time the pulse rate was 72, and the blood pressure, 135/85; there were single ventricular ectopic beats; the electrocardiogram showed a flat T_2 and a slurred QRS complex in Leads I, II, and III. One evening in September, 1943, as he was walking on the street, he suddenly felt a severe pain in the chest, became nauseated, and began to perspire excessively. When I saw him, a half hour later, he was pale, his skin was cool but wet with perspiration, and he complained that the pain was very severe. His pulse rate was 104, and his blood pressure, 160/90. An electrocardiogram was taken immediately, and was repeated daily for the next three days. The changes in the electrocardiogram were most definite between thirty-nine and sixty hours after the attack. The S-T segment was depressed in Lead I and in the left chest lead (CR_6) and elevated in Lead III. At that time, T was inverted in Leads II, III, and the right and left chest leads (CR_2, CR_6, and CR_8). The following morning (eleven hours after the attack), his temperature was 99° F., and the next morning, 100.4°; but, from the day after that, it remained normal (less than 99°). The sedimentation rate on the day after the attack was 18 mm. in two hours, and the leucocyte count before breakfast was 13,200 (83 per cent polymorphonuclears, 11 per cent lymphocytes, and 6 per cent monocytes). The blood pressure was 110/70, and remained at this level two days; on the third day it had risen to 120/75, and a week later was 130/80, at which level it was maintained. Whereas before the attack the pulse rate was always about 70, after the attack it rose to about 100 and remained at that level during the following ten days. Single ectopic beats (nodal type) and salvos of them were present on the second day, but after that and until the present writing no more have been found.

Received for publication Dec. 10, 1943.

philes. The sedimentation rate was 74 mm. in forty-five minutes. The sputum contained tubercle bacilli, Gaffky VII. The blood glucose and nonprotein nitrogen levels were normal.

A roentgenogram of the chest (Fig. 1) revealed almost complete collapse of the left lung, with encapsulated fluid at the level of the eighth rib posteriorly. In the right lung there was a diffuse, nodular type of infiltration throughout, more extensive in the upper and middle portions.

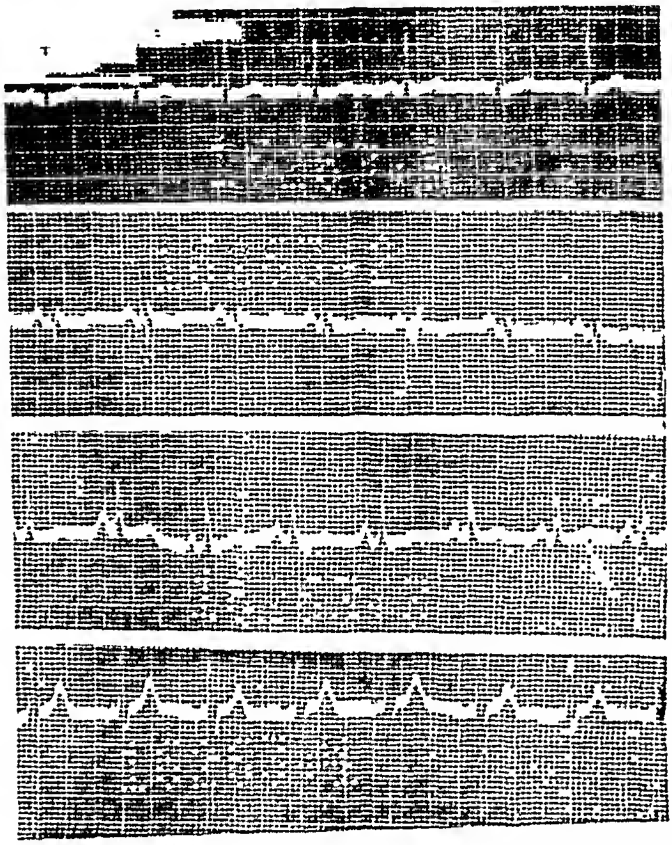


Fig. 2.—Electrocardiogram in July, 1943. Slurring of QRS complex and inversion of T wave in Lead II, with essentially normal tracings in other leads, indicative of cardiac rotation rather than myocardial damage.

Fig. 3.—Coronal section of the lungs. Silicotic foci throughout, many with secondary caseation. Compressed, interlocking excavation in left upper lobe. Almost entire left lung fibrotic and contracted. Left empyema space, with dense pleuropericardial adhesions.

we have observed three additional cases of silicosis and silicotuberculosis. In one of these, silicotic foci were found in the visceral pericardium and were apparently the etiological factor in the production of a noninfectious adhesive pericarditis. Since there was no evidence of silicosis in the myocardium, the lymph channels were probably the routes for the dissemination of the dust. In addition to the rarity of silicosis of the pericardium, this case illustrated the communication between pleural and pericardial lymphatic vessels.

CASE REPORT

History.—The patient, F. F., was a 51-year-old white man, a Spaniard by birth and a stonecutter by trade. He had noticed frequent "colds" and increasing dyspnea since 1936 and, in March, 1941, "streaked" blood for the first time. His local doctor diagnosed silicotuberculosis and instituted pneumothorax on the left side. He stopped work, remained at home, and was treated by the reinstitution of pneumothorax irregularly until November, 1942. At this time he had a large hemoptysis and was hospitalized; he was finally admitted to Sea View Hospital on Jan. 8, 1943. Since March, 1941, he had lost 22 pounds in weight and had experienced progressively increasing dyspnea. His past medical and family history were irrelevant.

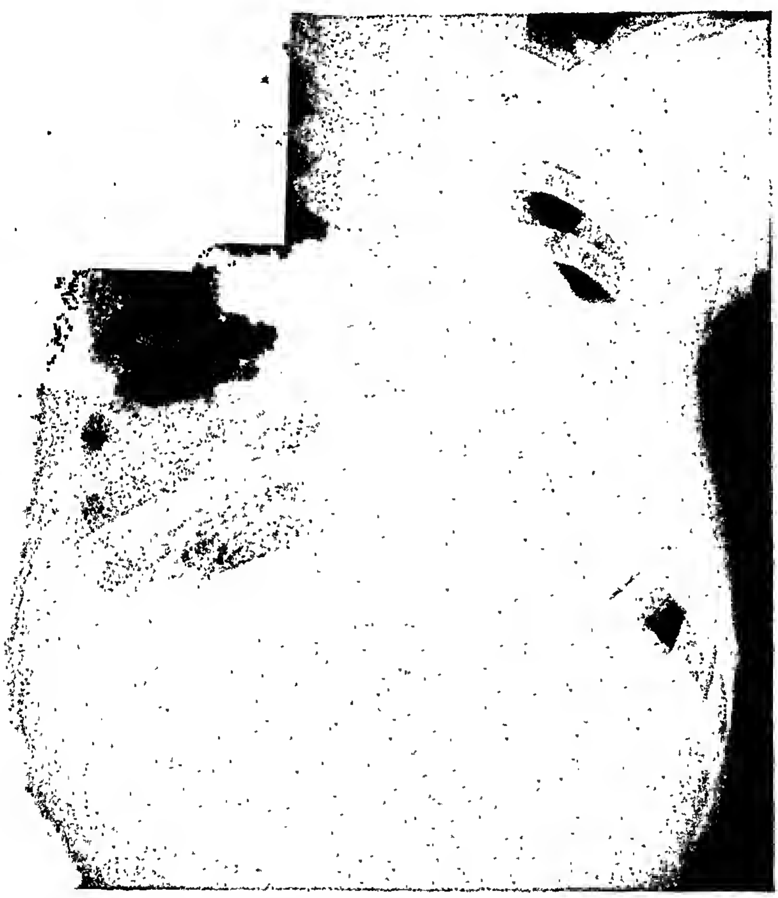


Fig. 1.—Roentgenogram made July 9, 1943. Encapsulated hydropneumothorax on the left. Marked retraction of the heart and mediastinum to the left. Spread to the right radiating from the hilum.

Physical Examination.—The patient was a well-developed, poorly nourished adult who appeared chronically ill. He was markedly dyspneic, but not cyanotic. There was moderate clubbing of the fingers. Other abnormalities were limited to the chest. There were signs of hydropneumothorax on the left side, with râles and bronchial breathing over the left upper lobe. The right lung was normal. The heart was normal in size, the rate was 90 per minute, and the rhythm was normal. There was a soft systolic murmur at the apex, transmitted to the axilla.

The urine had a specific gravity of 1.010 and was normal except for occasional leucocytes. The blood Wassermann reaction was negative. The erythrocyte count was 4,100,000, the hemoglobin, 78 per cent, and the leucocyte count, 8,500, of which 68 per cent were polymorphonuclear leucocytes, 3 per cent nonsegmented polymorphonuclear leucocytes, 17 per cent lymphocytes, 8 per cent monocytes, 1 per cent eosinophiles, and 1 per cent baso-

firm, fibrous adhesions revealed silicotic foci within the visceral pericardium (Fig. 4). There were no cellular or other abnormalities suggestive of an infectious process in the pericardium. There were no silicotic foci in the myocardium.

Other lesions included miliary tubercles of the spleen and kidney and tuberculous ulcerations of the ileum and larynx. The liver weighed 1,640 grams, and the spleen, 375 grams. The peripancreatic lymph nodes contained silicotic foci similar to, but less extensive than, those of the tracheobronchial nodes.

COMMENT

In their extensive studies of pneumoconiosis, Gardner,[2] Cummins,[3] and others have repeatedly emphasized the importance of blockage of the lymphatic channels by dust thrombi and the resulting fibrosis. Since, however, this blockage probably occurs chiefly in the lymphatic vessels of the tracheobronchial nodes, there remains a possible exit for silica particles in the peripheral (pleural) lymphatic vessels. Although retrograde lymph flow from the tracheobronchial nodes along the afferent channels from the pericardium is possible, the early obstruction within the nodes makes this unlikely. Since the lymphatic vessels from the peripheral portions of the lungs, which are affected by silicosis last, drain towards the pleura and not the hilum, they may remain patent long after the deep lymphatic vessels have been blocked.

These superficial lymphatic vessels, like those of the deep channels of the lung, the heart, and the pericardium, ultimately reach the mediastinum. However, when the pleura and pericardium are adherent there is probably free communication between the lymphatic vessels of the two. This was true in this case; the adhesions were present over a wide area posteriorly. Obviously, the more extensive the adhesions between the pleura and pericardium, the greater will be the lymph exchange. How extensively the adhesions develop depends chiefly upon the pulmonary lesions. In this case there was almost complete destruction of intrapulmonary elastic fibers by a combination of silicotic and tuberculous fibrosis. Because of its loss of resiliency, the lung occupied a much smaller space than previously, and the mediastinal structures were retracted into the left side of the chest, giving the pericardium greater opportunity to adhere to the pleura.

Neither the retraction nor the pleuropericardial adhesions are uncommon in tuberculosis, particularly with left-sided involvement. In uncomplicated silicosis and in silicotuberculosis, however, since the lungs are usually voluminous, marked retraction is unusual. The encapsulated pneumothorax in this case was large enough to augment the intrapulmonary tendency of the lung to retract, but not great enough to prevent the heart's being withdrawn into the left hemithorax.

Why the silicosis of the pericardium should lead to adhesive pericarditis is difficult to understand. The firmest attachments were at the site of the densest pleuropericardial adhesions, at which point the pleura and both the visceral and parietal pericardium were as one. Probably both the physical and irritative characteristics of the siliceous particles were responsible for the development of these adhesions.

Except for the abnormal electrocardiogram, there was no subjective or objective evidence of cardiac disease. It is likely, however, that, had the patient survived, the pericardial silicosis would have progressed, as silicosis progresses in the lungs and lymph nodes, and cardiac embarrassment might have developed.

Course.—Because of the dyspnea and the ineffectiveness of the pneumothorax, the latter was discontinued. Six weeks after admission, generalized petechiae of the lower extremities appeared. The platelet count at this time was 289,720, and the blood picture was essentially the same as on admission. The liver and spleen were not felt, and the petechiae disappeared spontaneously after about four weeks. The electrocardiogram at this time showed inversion of the T wave and slurring of the QRS complex in Lead II. Since there was retraction of the heart into the left side of the chest, with probable rotation, this could not be interpreted as evidence of myocardial damage (Fig. 2).

In spite of aspiration of fluid from the left pleural sac, the patient became increasingly dyspneic. In April, 1943, the temperature rose to 101° to 102° F., and there was evidence of extensive bronchogenic spread to the right lung. On Sept. 7, 1943, he spat up two ounces of blood, and died Oct. 12, 1943, of progressive pulmonary insufficiency. Terminally there were marked dyspnea and cyanosis, but no edema. The abdomen was soft, but diffusely tender. No solid organs were palpable.

Fig. 4.—Photomicrograph of left ventricle. Silicotic focus in the pericardium adjacent to a large blood vessel at the site of dense adhesive pericarditis. No foci in the myocardium.

Autopsy.—The lungs weighed 3,510 grams. The small, residual left pleural space was filled with 300 c.c. of yellowish-green fluid containing large amounts of fibrin. The pleural space was obliterated over most of the left lung, and the visceral and parietal pleurae were markedly thickened. The pleura over the right lung was also thickened, although to a less extent, and the pleural space was completely obliterated. Section of the left lung showed that it was almost completely occupied by conglomerate silicotic foci (Fig. 3). In the left upper lobe there was a large, elliptical, tuberculous excavation measuring 7.5 cm. in its largest, apicobasal direction. The right lung was studded with silicotic foci measuring from 3 to 10 mm. in diameter. A tuberculous cavity, 1 cm. in diameter, was present in the upper lobe. The tracheobronchial and peribronchial lymph nodes were from 1 to 3 cm. in diameter and were almost completely occupied by silicotic foci.

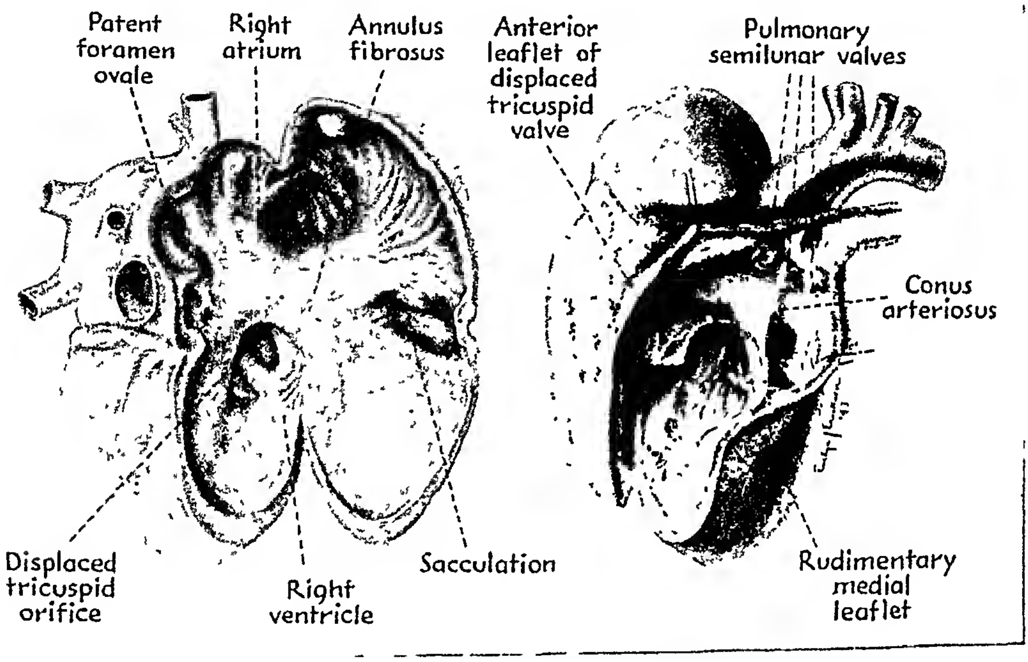
The heart, without the pericardium, weighed 360 grams. The pericardial cavity was completely obliterated by thin, fibrous adhesions, except over the atria and a portion of the left ventricle posteriorly, where the adhesions were thick, firm, and impossible to separate except by sharp dissection. The parietal pericardium was adherent almost completely to the left parietal pleura posteriorly. A patent foramen ovale admitted the tip of a probe. The right ventricular wall measured 8 mm. in thickness, and the left, 11 millimeters. There was moderate atheromatosis of the coronary arteries and aorta. There was no evidence of infarction, but microscopic examination of the left ventricle in the region of the

There was no fluid in the pleural cavities. Each lung weighed 30 grams. Crepitation was diminished in the lower lobes. A moderate amount of blood exuded from the cut surface.

The thymus was normal in size and appearance.

The pericardial sac was normal in appearance, and contained no excess fluid.

The heart, which weighed 53 grams and measured 5.5 cm. in its greatest transverse diameter, showed marked enlargement of the right auricle and right ventricle and a rounding of the apex. The interventricular and atrioventricular sulci were distinct. Opening the heart revealed patency of the foramen ovale; it measured 1.2 cm. in its greatest diameter. The right auricle was hypertrophied and its wall well trabeculated. The right atrioventricular orifice, 7 cm. in circumference, showed no tricuspid leaflets around its margin. A fibrous ridge extended along the posterior septal margin of this orifice and became continuous with the base of a membranous leaflet which was deflected medially and attached to the anterior wall of the conus arteriosus. The free border of this membrane formed the lateral margin of an orifice leading into the conus arteriosus. This membranous structure, which represented the anterior leaflet of the malformed and displaced tricuspid valve, divided the right ventricle into two portions. The larger portion was thrown into the cavity of the right auricle, and the remaining portion formed a smaller chamber which



A. B.

Fig. 1.—*A*, Drawing of the right atrium and ventricle, which have been opened to show the absence of tricuspid segments around the atrioventricular margin. Note the abnormal position of the tricuspid orifice produced by the malformed segments. *B*, Drawing of the right ventricle, which has been opened through the displaced tricuspid orifice to show the malformed segments and the separation of the right ventricle into two chambers.

included the conus arteriosus. The orifice leading into the second chamber was bounded laterally by the membranous leaflet, and medially by a fibrous ridge which extended along the interventricular septum to the anterior wall of the conus arteriosus. Below the fibrous ridge on the septum was a small pocketlike mass of endocardial tissue which represented the rudimentary septal leaflet of the tricuspid valve. The posterior leaflet was entirely unformed. There were no defects in the interventricular septum. The pulmonary orifice measured 8 mm. in circumference, and its cusps were normal. There was a saccular outpouching of the posterior lateral wall of the right ventricle, which in this area was very thin. The posterior portion of the interventricular septum was well trabeculated, but the remainder of the right ventricle had a smooth, dull lining. Examination of the left ventricle showed that the mitral leaflets, chordae tendineae, and papillary muscles were normal in appearance. The aorta and great vessels showed no abnormalities. The ductus arteriosus was closed and persisted as a thin fibrous cord.

The peritoneal cavity contained no free fluid. The liver weighed 25 grams, and a large amount of blood escaped from the cut surface. The other organs showed no gross abnormalities.

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CONGENITAL TRICUSPID INSUFFICIENCY

Report of a Case

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CONGENITAL tricuspid insufficiency is a rare cardiac anomaly. In an analysis of one thousand cases of congenital cardiac disease, Abbott[1] listed five cases of congenital tricuspid insufficiency in which this defect was classified as the primary lesion. She described two anatomic types of this lesion: (1) incomplete differentiation of the cusps, and (2) the Ebstein type in which the undifferentiated tricuspid segments are represented by a membranous diaphragm displaced downward toward the apex of the right ventricle. The latter type, first described by Ebstein in 1866, is a well-defined lesion. Sixteen cases belonging to this group are recorded in the literature. These cases present various degrees of differentiation of the tricuspid segments, but common to all of them is the abnormal position of the malformed segments. The segments are not located around the right atrioventricular orifice, but are displaced downward toward the apex of the right ventricle, so that a portion of the right ventricle is drawn into the right auricle, and both chambers are dilated. In all but two cases, this anomaly was associated with patency of the foramen ovale.

A case of congenital tricuspid insufficiency of the Ebstein type is reported.

REPORT OF CASE

The patient, a white, 8-month-old, female infant, was well until a few days before admission to the hospital. At that time she developed an infection of the upper respiratory tract and became dyspneic and cyanotic. The mother stated that prior to this illness the patient had become cyanotic only during crying spells.

On admission the temperature was 97° F., the pulse rate, 160, and the respirations, 78. Examination of the chest revealed no abnormality of the lungs. There was marked enlargement of the heart. No definite murmurs were heard. The cardiac rhythm was regular.

Roentgenologic studies of the chest revealed marked enlargement of the cardiac silhouette involving both ventricles, but particularly the right. The lungs were normal, and there was no evidence of obstruction of the trachea or narrowing of the bronchi. The hemoglobin was 78 per cent; the erythrocyte count was 4,100,000 per c.mm.; and the leucocyte count was 12,200 per c.mm., with 41 per cent neutrophiles.

The patient remained cyanotic after admission to the hospital, and became increasingly dyspneic. She was given oxygen continuously, and died three days after admission.

Post-mortem examination revealed a well-nourished, 8-month-old, white female infant showing cyanotic discoloration of the face, neck, and extremities, but no external malformations.

Received for publication Feb. 14, 1944.

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Abstracts and Reviews

Selected Abstracts

Gross, D.: **Psychophysiologic Studies of the Cardiac Patient.** Rev. méd. de Chile 68: 258, 1944.

An attempt is made to evaluate the influence that circulation has on the brain observing the changes in psychic functions when the circulation is impaired. For this purpose the author studies the circulation time and the results of different psychic tests in patients with congestive failure and after improvement. The circulation time from arm to tongue was measured with calcium bromide. Psychic tests measured concentration, association, attention, optic orientation, and resistance to, and individual rhythm of, mental work.

This study shows that there is no exact proportion between the speed of circulation and the speed of mental functions. However, congestive failure causes a marked decrease of all mental functions, so that values of patients normally quick become similar to those of people normally slow.

A quotient between circulation time and either association time or Schulte's test is described. It gives a kind of mathematical evaluation of the single patient independent of transitory changes due to heart failure.

A. Luisada.

Fox, T. T.: **Aberrant Atrio-Ventricular Conduction in a Case Showing a Short P-R Interval and an Abnormal But Not Prolonged QRS Complex.** Am. J. M. Sc. 209: 199, 1945.

A case is presented with a short P-R interval and an abnormal but not prolonged QRS complex. Prolongation of the QRS complex was achieved through the influence of cholinergic drugs. In this manner the syndrome of short P-R interval and prolonged QRS complex was reproduced. It would therefore appear that the width of the QRS complex in this syndrome is merely an expression of the quantity of "vagus substance" available, and that the actual criteria of the Wolff-Parkinson-White syndrome are: a short P-R interval and an abnormal but not necessarily prolonged QRS complex.

In view of this, and of the available histologic evidence of the existence of an aberrant A-V conduction pathway, it is suggested that the syndrome be known as the "aberrant atrio-ventricular conduction."

Author.

Cossio, P., Vedoya, R., and Berconsky, I.: **Modifications of the Electrocardiogram After an Attack of Paroxysmal Tachycardia.** Rev. argent. de cardiol. 11: 164, 1944.

The electrocardiographic alterations which appear after an attack of paroxysmal tachycardia and which constitute an electrocardiographic syndrome were studied in two personal observations and twenty similar cases found in the literature.

This posttachycardiac syndrome is characterized by negative displacement of the S-T segment, inversion and widening of the T wave, and lengthening of the Q-T interval. It appears especially after attacks of ventricular paroxysmal tachycardia (sixteen cases). A relation was found between the situation of the automatic focus which originates the ventricular tachycardia and the lead automatic focus which originates the ventricular tachycardia and the lead (I or III) in which the electrocardiographic changes appear.

A functional alteration of the automatic ventricular focus, persisting after the attack is over, may be the cause of the posttachycardiac syndrome.

Authors.

COMMENT

In this case, as in similar cases which have been reported, the anomaly involved only the right atrioventricular valve. Similar cases have been reported by Ebstein,[2] MacCallum,[3] Heigel,[4] Marxsen, Geipel, Schonenberger, Malan, Morison,[5] Abbott,[6] and Arnstein.[7] These cases present various degrees of differentiation of the tricuspid segments, but the feature common to all of them is the abnormal position of the malformed segments which results in a herniation of the larger portion of the right ventricle into the cavity of the right auricle. As stated by Heigel[4] and Arnstein,[7] the similarity among the cases rests in the following facts: that the medial leaflet is incompletely formed and in most instances is represented by a rudimentary tag; that the anterior leaflet is the largest, is abnormal in shape, and in some instances is represented by a fenestrated membrane; and that the posterior leaflet is most affected in the anomaly, and, if formed at all, is rudimentary. Heigel states that these changes must be due to malformation, because an inflammatory process, even fetal, could not produce this type of anomaly so uniformly.

In the case presented, the pseudovalvular orifice below the conus arteriosus had no valvular function, so that, anatomically and functionally, this represents a true tricuspid insufficiency.

SUMMARY

An unusual cardiac anomaly, presenting defective and displaced tricuspid valvular segments and a large, patent foramen ovale, is reported. This belongs to the type of congenital tricuspid insufficiency designated as Ebstein's disease.

REFERENCES

1. Abbott, M. E.: Atlas of Congenital Cardiac Disease, New York, 1936, The American Heart Association, pp. 61 and 24.
2. Ebstein, W.: Ueber einen seltenen Fall von Insufficienz der Valvula tricuspidalis, bedingt durch eine angeborene hochgradige Missbildung derselben, Arch. f. Anat. u. Physiol. vol. 238, 1866.
3. MacCallum, W. G.: Congenital Malformations of the Heart as Illustrated by the specimens in the Pathological Museum of the Johns Hopkins Hospital, Bull. Johns Hopkins Hosp. 11: 69, 1900.
4. Heigel, A.: Ueber eine besondere Form von Entwicklungsstörung der Trikuspidalklappe, Arch. f. path. Anat. 214: 301, 1913.
5. Morison, A. B.: Malformed Heart With Redundant and Displaced Tricuspid Segments and Abnormal Attenuation of the Right Ventricular Wall, J. Anat. 57: 262, 1922-1923.
6. Abbott, M. E.: Blumer's Bedside Diagnosis, Philadelphia, 1928, W. B. Saunders Co., vol. 2, p. 482.
7. Arnstein, A.: Eine seltene Missbildung der Trikuspidalklappe, Virchows Arch. f. path. Anat. 266: 247, 1927.

the third the situation was in doubt. Further experience is necessary before an opinion can be expressed regarding the value of heparin as an adjuvant to penicillin in the treatment of this disease.

AUTHORS.

Tinsley, C. M.: Pneumococcic Endocarditis. Arch. Int. Med. **75:** 82, 1945.

Pneumococcic endocarditis occurs in about 3 to 3.5 per cent of all pneumococcic infections and is probably responsible for about 5 to 10 per cent of deaths due to pneumococcic infections. The aortic and mitral valves are infected in 36 and 33 per cent of the cases, respectively. In only approximately 11 per cent of the cases are the valves of the right side of the heart solely involved. Antecedent valvular damage is present in a minority of the instances but is present often enough—perhaps in one-third of the cases—that it may well contribute to the development of this disease. Purpura, splenomegaly, and infarction of organs by emboli are less common than in subacute bacterial endocarditis. The ulcerative infectious process often produces fenestration of a valve cusp, with subsequent appearance of the murmur of aortic insufficiency. A thorough search for this murmur should be made in every case of pneumococcic infection which does not give evidence of rapid and complete recovery. Pneumococcemia is almost invariably present, and repeatedly positive blood cultures are presumptive evidence of the existence of this disease. The disease is usually rapidly fatal and may terminate in acute purulent meningitis. Treatment has so far been highly unsatisfactory.

AUTHOR.

Guy, P. F.: Rheumatic Fever of Childhood. Northwest Med. **43:** 166, 1944.

Problems encountered in the diagnosis of 178 cases of rheumatic fever admitted to the Children's Orthopedic Hospital of Seattle are itemized. The five manifestations of rheumatic fever are discussed and the abstract of a case history including all five is given. The onset of rheumatic fever and the frequency of a preceding episode in the 178 cases is analyzed and reference is made to the part played by the *Streptococcus hemolyticus*. The value of continuous institutional care during the toxic period is discussed. Tonsillectomy in rheumatic fever patients, the age of onset, and other observations are analyzed.

AUTHOR.

Fashena, Gladys J.: The Incidence of Rheumatic Fever in Texas With Particular Reference to the Dallas Area. Texas State J. Med. **39:** 474, 1944.

The morbidity and mortality statistics quoted from the Children's Medical Center must be interpreted with caution since there are a number of factors which serve to weight the data. The fact that a children's cardiac clinic is in operation at the center serves to attract cardiac referrals from out of town as well as from other hospitals in the city. The mortality statistics are weighted by the fact that the hospital admits no contagious diseases and relatively little traumatic or brain surgery. Nevertheless, taking all factors into consideration, we feel that certain inferences can be drawn from the material presented here.

The official mortality statistics appear to show that the 1941 death rate from rheumatic fever in Texas in the school-age period is not strikingly less than in the so-called "rheumatic fever states." The hospital data indicate that rheumatic fever can scarcely be termed a rare disease in the Dallas area. It is believed that the disease, although probably somewhat less frequent than in the northern United States, constitutes a larger cause of morbidity and mortality in the Dallas area and probably in Texas as a whole than is generally appreciated.

AUTHOR.

Bruetsch, W. L.: Late Cerebral Sequelae of Rheumatic Fever. Arch. Int. Med. **73:** 472, 1944.

A late sequel of rheumatic fever is obliterating endarteritis, which usually develops while the patient is otherwise in good health. If the vascular process involves the small meningeal and cortical vessels, gross and microscopic infarctions in the gray matter of the brain will result, producing a variety of mental symptoms.

Battro, A., Aguirre, R. C., and Mendy, J. C.: Electrocardiographic Studies in Heine-Medin's Disease (Poliomyelitis). Rev. argent. de cardiol. 11: 185, 1944.

Of thirty-eight cases of poliomyelitis observed during the acute stage, four showed electrocardiographic alterations which appear to be the expression of cardiac damage. The clinical examination did not reveal any abnormality apart from a moderate tachycardia. The facts: (1) that these electrocardiographic alterations disappeared in the course of the illness and (2) that none of the eighteen chronic cases showed electrocardiographic alterations indicate that the cardiac complication was, in these cases, of a transient nature and related to the acute period of poliomyelitis.

AUTHORS.

Manning, G. W., and Stewart, C. B.: Alteration From Normal to Abnormal P-R Interval With Change in Posture. Canad. M. A. J. 51: 546, 1944.

In three of the cases which were observed among aircrew trainees the P-R interval was reduced from 0.28, 0.24, and 0.24 seconds, respectively, to 0.20 seconds on changing from the recumbent to the sitting position. These changes occurred without any significant alteration in heart rate. In the fourth case the P-R interval was 0.40 seconds taken in the recumbent position and 0.20 seconds taken in the sitting position with no change in heart rate. Four years later there was no significant change. The P-R interval could be reduced to normal by excessive exercise in the recumbent position or by assuming the upright position.

MCCULLOCH.

Shapiro, M. J.: The Preoperative Diagnosis of Patent Ductus Arteriosus. J. A. M. A. 126: 934, 1944.

The diagnosis of patent ductus arteriosus can be made without error. Patients should not be referred for surgical treatment unless they show the characteristic machinery murmur. The only exception to the rule is the occasional patient with a large patent ductus who may exhibit no murmurs. Patients with cyanosis and clubbing of the fingers do not have uncomplicated patent ductus. They cannot be treated surgically. Pronounced electrocardiographic changes are not part of the picture of simple patent ductus arteriosus.

AUTHOR.

Coulter, W. W., and Marcuse, P.: Acute Isolated Myocarditis. Am. J. Clin. Path. 14: 399, 1944.

A case is reported in which a nonspecific type of myocarditis and less marked nonspecific changes in the lungs and liver were the pathologic findings. The lesions in the heart muscles were severe enough to account for the patient's sudden death after a short illness with vague symptoms.

AUTHORS.

Dawson, M. H., and Hunter, T. H.: The Treatment of Subacute Bacterial Endocarditis With Penicillin. J. A. M. A. 127: 129, 1945.

Twenty patients with subacute bacterial endocarditis were treated with penicillin. A preliminary group of five patients was treated in 1942 and 1943, and a group of fifteen was treated in 1944. The infecting organism was a streptococcus in all instances. Heparin was employed as an adjuvant to penicillin in the treatment of the majority. While it is recognized that a long follow-up will be necessary before the ultimate outcome is established, therapy was apparently successful in fifteen of the twenty patients. All fifteen patients are now clinically and bacteriologically free from infection. In two of the remaining five patients the infection was controlled as long as penicillin was administered, but a relapse occurred when therapy was discontinued. These two patients are still in excellent general health, and it is hoped that it will yet be possible to arrange for a therapeutic regimen which will produce a satisfactory outcome. The remaining three patients succumbed. In each instance death was apparently due to a cerebral embolus. In two of the fatal cases the infection was still present at the time of death, and in

blood pressure was essentially the same (29.2 per cent) as in the 1-year-old group. The systolic blood pressure for 2-year-old vitamin E deficient rats and normal control rats was 61.7 mm. and 87.2 mm., respectively. A lowering of the blood pressure in the second year of life is reflected equally in both experimental and control groups. This reduction is therefore due to an aging effect and is not a manifestation of a dietary deficiency. An histologic examination of the hearts and large vessels of vitamin E deficient rats failed to demonstrate any consistent vascular lesions that might contribute to a reduction of blood pressure. Variations in the room temperature, age and sex of the animal, and methods used in determining blood pressure are variables that influence the blood pressure readings in normal and experimental rats.

AUTHORS.

Quinby, W. C., Dexter, L., Sandmeyer, J. A., and Haynes, F. W.: The Renal Humoral Pressor Mechanism in Man. II. The Effect of Transitory Complete Constriction of the Human Renal Artery on Blood Pressure and on the Concentration of Renin, Hypertensinogen, and Hypertensinase of Renal Arterial and Venous Blood, With Animal Observations. J. Clin. Investigation 24: 69, 1945.

Complete constriction of the renal artery in five patients and in six dogs, for a period of twelve minutes, produced no rise in blood pressure after release of the clamp but did liberate small amounts of renin into the renal venous blood of the two patients in whom it was estimated and in two of six dogs.

In patients, the concentration of hypertensinogen was the same in the renal arterial and venous blood, before and after constriction of the renal artery, with one exception; hypertensinase, determined at a pH of 7.3 and 4.5, was likewise the same.

These observations demonstrate that by constriction of the renal artery in man, the renal humoral pressor mechanism is stimulated to activity as in animals.

AUTHORS.

Haynes, F. W., and Dexter, L.: The Renal Humoral Pressor Mechanism in Man. III. The Hypertensinase Content of Plasma of Control Subjects and of Patients With Hypertension and Other Diseases. J. Clin. Investigation 24: 75, 1945.

The hypertensinase content of nonhemolyzed plasma of ten normal subjects ranged from 1.1 to 1.8 dog units per milliliter of plasma. The hypertensinase content of the plasma of sixteen patients with hypertension, six patients with nitrogen retention, two patients with Addison's disease, and three patients with hepatic disease did not differ from the normal. It is concluded that there is no justification for considering that the blood pressure is high in human hypertension because of a deficiency of hypertensinase in plasma.

AUTHORS.

Grollman, A.: Experimental Chronic Hypertension in the Rabbit. Am. J. Physiol. 142: 666, 1944.

The blood pressure of adult rabbits was followed for three months or more following various operative procedures on the kidneys. The average rise in blood pressure following unilateral compression of the kidney did not exceed that which followed unilateral nephrectomy. Removal of the compressed kidney in a hypertensive animal did not result in lowering of the blood pressure. Rabbits may exhibit hypertension even in the absence of all renal tissue.

The implications of the observed results on the author's concept of the mechanism of experimental renal hypertension are discussed. In the rabbit, as in the rat, the available data support the view that chronic hypertension results from a deficiency induced by injury or removal of normal renal tissue and not from the formation of a renal pressor substance. The latter, however, may play a part in causing hypertension in the acute experiment.

AUTHOR.

This type of cerebral involvement has been termed "rheumatic brain disease." It represents a chronic infectious process in the same sense as rheumatic heart disease.

Although widespread and clinically manifest obliterating arteritis seems to occur in only a small number of patients with rheumatic heart disease, the possibility of the development of rheumatic endarteritis in such a person appears to be ever present.

Rheumatic fever in the form of this late cerebral sequel has been found to be an important factor in the causation of mental illness. The fact that rheumatic heart disease is several times more frequent among mentally ill patients than in persons of the general population emphasizes this contention.

Other late cerebral sequelae of rheumatic fever are rheumatic encephalitis and cerebral embolism, the latter occurring most often during auricular fibrillation in patients with mitral stenosis.

AUTHOR.

Webb, A. C.: Periarteritis Nodosa in Pregnancy. Arch. Path. 38: 329, 1944.

Periarteritis nodosa was observed in a parturient woman whose death most probably can be ascribed to severe toxemia and puerperal sepsis. The role played by the lesions of periarteritis nodosa in relation to the death of the patient cannot be evaluated.

AUTHOR.

Smirk, F. H.: Casual and Basal Blood Pressures; IV. Their Relationship to the Supplemental Pressure With a Note on Statistical Implications. Brit. Heart J. 6: 176, 1944.

The casual blood pressure may be regarded as the sum of the basal blood pressure and the supplemental pressure; this last represents the degree of blood pressure elevation above the basal level due to whatever degree of physical, emotional, and suprabasal metabolic activity is present at the time of blood pressure measurement. The basal pressure is the pressure measured at a time when physical, emotional, and metabolic activity are reduced to a physiologic minimum. In cases where it is impossible to do this because of restlessness or emotional tension, the reading obtained should not be described as basal. Failure to obtain the true basal reading will not always be apparent to the observer especially when, as is most commonly the case, the failure is due to emotional reasons.

Both normal and hypertensive subjects with a high basal pressure have a greater statistical expectation of having a high casual pressure than do those whose basal pressure is low. Likewise those with high supplemental pressures have a greater statistical expectation of a high casual pressure than do those whose supplemental pressure is low.

In comparing one individual with another the basal and supplemental pressures are independent variables in the sense that the level of the basal blood pressure in an individual is no guide to the probable level of the supplemental pressure.

Most statistics concerning the level of the blood pressure are concerned with the casual readings. The fact that, when comparing one individual with another, within a comparable physiologic group, the casual blood pressure is to be regarded as the sum of two independent variables has statistical implications which are discussed.

The supplemental pressure forms a significantly higher proportion of the casual pressure among patients with essential hypertension than among normal subjects.

An improved method is recommended for determining the basal blood pressure.

AUTHOR.

Telford, I. R., Swegart, J. E., and Schoene, F. C.: Blood Pressure Studies on Normal and Vitamin E Deficient Rats. Am. J. Physiol. 143: 214, 1945.

One-year-old vitamin E deficient female rats showed a reduction of 29 A per cent in their systolic blood pressure when compared with normal rats of the same age (78.2 mm. : 110.8 mm.). In 2-year-old vitamin E deficient rats the reduction in

good flow even at this low level of pressure, whereas in some instances a sluggish flow was present in the mesenteries of some dogs even when the blood pressure was as high as 60 mm. of mercury.

Following such large hemorrhages, direct observations showed that the corpuscles in the vessels were separated by more than the normal amount of plasma. At arterial pressures of 30 to 40 mm. Hg, the intestine became bluish red, in contrast to its normal pink color during control periods.

Albumin infusions given into an artery after the pressure had been kept at 30 to 35 mm. Hg for half an hour restored the blood flow, caused the constricted arteries and arterioles to relax, the blood pressure to rise, and the intestine and tongue to return approximately to their normal colors. This was similar to the changes observed when the blood previously withdrawn was returned.

AUTHORS.

Baker, E. C., and Miller, F. A.: Further Experiences With Venography. Radiology 43: 129, 1944.

The authors described a method of venography which, in their hands, has given practically complete visualization of the veins of the entire leg, thigh, and lower pelvis in most cases. The venograms are classified into types or patterns, indicating acute and chronic block of the superficial and of the deep plexuses. Three types of venous thrombosis have been observed and described. Four methods of abnormal venous return from the thigh to the body have been demonstrated. They believe that the procedure, when properly done, gives highly accurate information.

AUTHORS.

Jones, J. C., and Thompson, W. P.: Arteriovenous Fistula of the Lung. J. Thoracic Surg. 13: 357, 1944.

Arteriovenous fistula of the lung produces a syndrome characterized by cyanosis, clubbing of fingers and toes, symptomatic polycythemia, and symptoms of anoxemia, usually in a young patient with an obscure lung tumor and a normal heart. A continuous murmur may be heard over the tumor.

The treatment is resection of the fistula or pulmonary resection, either of the lobe or the entire lung.

The case of a patient with arteriovenous fistula of the right lung cured by pneumonectomy is reported in detail.

AUTHORS.

Enikeeva, S. I.: The Mechanism of Epinephrine Bradycardia and Shock in Young Animals. Am. J. Physiol. 143: 134, 1945.

Puppies less than 45 days old whose vagus centers show neither tonic activity nor reflex excitability respond with cardiac acceleration to small doses and cardiac slowing to large doses of epinephrine. Puppies and young rabbits show these responses after section of both vagi but the slowing does not occur after sympathectomy. Epinephrine bradycardia is through sympathetic innervation in very young animals.

Epinephrine bradycardia is reversible if the dose is not too large. If the dose exceeds the fatal dose for adults by eight to ten times, the young animal will die in thirty to one hundred eighty minutes. Death in two to four minutes, characteristic of the adult rabbit, occurs in the young rabbit only if the dose is twenty to thirty times the lethal dose for the adult.

Young rabbits do not show lung edema after epinephrine as do adults, though it may be produced in the young rabbit by lung irritants.

AUTHOR.

Rimmerman, A. B.: Digilanid and the Therapy of Congestive Heart Disease. Am. J. M. Sc. 209: 33, 1945.

Digilanid, a complex of lanatosides A, B and C, the pure glycosides of *Digitalis lanata*, adjusted by weight, was studied in twenty-seven cases of congestive heart failure. Our investigation proves digilanid to be an effective cardio-active prepara-

Hueper, W. C.: Experimental Studies on the Therapy and the Prevention of Degenerative Vascular Diseases. II. The Effects of Several Detergents on Experimental Cholesterol Atheromatosis of Rabbits. Arch. Path. 38: 381, 1944.

Tergitol Penetrant 08 and Nacconol FSNO given by mouth elicited degenerative and calcifying lesions in the aortas of normal rabbits in addition to causing pulmonary edema, hyperemia and hemorrhages, and pleural effusion. Triton K-60 given by the same route did not produce any vascular reactions.

Similar pulmonary responses were seen in rabbits following repeated intravenous injections of Nacconol NRNO, while rabbits given injections of Triton NE exhibited marked irritation of the intestine. Rabbits into which Nacconol NRNO or Aerosol OT had been injected intravenously showed hyaline degenerated cerebral arteries and renal arterioles. Carcinomatoid proliferations were found in the lungs of rabbits fed Triton K-60 and Nacconol FSNO as well as in a cholesterolized rabbit given injections of Aerosol OT.

Following repeated oral administration of Aerosol OT, Triton NE and lithium iodide plus potassium thiocyanide in rabbits fed daily 0.5 Gm. of cholesterol in oil, it was noted that Aerosol OT seemed to interfere to some degree with the development of hypercholesteremia and atheromatosis, whereas Triton NE and lithium iodide plus potassium thiocyanide appeared to hasten and aggravate these processes.

Some of the evidence suggests that in certain respects there is an antagonism between the factors favoring atherosclerosis and those active in the production of thrombosis related to the wettability of the vascular wall, the circulatory conditions, and possibly also the oxygen-carbon dioxide tension of the blood.

AUTHOR.

Alberti, V. A. J., Segura, R. G., and Lanari, A.: Influence of Diminution of Intrathoracic Pressure on Blood Pressure in the Two Circulations. Medicina, Buenos Aires 5: 35, 1944.

The pressure changes in cats, with an endotracheal aspiration, were studied with regards to the aorta, the pulmonary artery, and both ventricles. The pressure readings were performed with Hamilton's manometer and through a thoracic puncture. The endothoracic depressions that occurred were about 30 cm. of water.

Negative pressures were registered in the pulmonary artery and in the right ventricle, without fall in the pulse pressure. The thoracic aortic pressure did not change, and, regarding the left ventricle, the systolic pressure was steady, while the diastolic was negative and similar to the right ventricle.

The etiology of these changes and their relationship to the pulmonary circulation in lung atelectasis are discussed.

AUTHORS.

Page, I. H., and Abell, R. G.: Effects of Acute Hemorrhage and of Subsequent Infusion Upon the Blood Vessels and Blood Flow as Seen in the Mesenteries of Anesthetized Dogs. Am. J. Physiol. 143: 182, 1945.

The method used in these experiments was to bleed the dogs acutely at short intervals until the pressure fell to 30 to 35 mm. Hg, and to maintain the animal in that state for thirty to forty-five minutes. Direct microscopic observations of the vessels in the mesentery of the dog showed that the arteries (0.39 to 1.2 mm. control diameters) constricted 20 to 60 per cent following removal of 2.5 to 5.5 per cent of the body weight of blood. The arterioles (24 to 65 diameters) usually constricted to a like degree, though sometimes slightly more. In many instances the larger veins (1 to 2.1 mm.) also constricted, the degree being from 12 to 43 per cent. The venules (160120) did not constrict; in some instances they dilated to 1.1 to 1.2 of their control diameters. The capillaries were not observed either to constrict or dilate. No measurements were made of arterioles having diameters of less than 24.

At hypotensive levels of about 30 mm. Hg, produced in these experiments by the removal of 3.5 to 5.5 per cent of the body weight of blood, the arterial flow was usually slow and pulsatile. Sometimes it was intermittent. Stasis was frequently present in some of the venules. For the most part the capillary bed was ischemic. Some variation occurred, however, and an occasional dog maintained a moderately

Book Reviews

The Foetal Circulation and Cardiovascular System, and the Changes That They Undergo at Birth. By Alfred E. Barclay, Kenneth J. Franklin, and Marjorie M. L. Prichard, Nuffield Institute for Medical Research, Oxford. Blackwell Scientific Publication, Ltd., Oxford, 1944, pp. xvi and 275, 160 illustrations, some in color; 50 shillings.

This monograph is a most interestingly written account of the fetal cardiovascular system and the circulation of the blood in one particular species of animals—the sheep—with a general discussion of this subject in other forms, especially in man. In it are brought together the results of a long series of painstaking experiments performed by a group of physiologists at Oxford, England, with the co-operation of their colleagues at Cambridge. It is definitely the most complete piece of work of its kind. The subject of the circulation through the heart of the fetus is a very old one. It is doubtful whether any subject in embryology has provoked so much discussion. Whether there is a separation or a complete mixing of the superior and inferior caval blood stream in the fetal right atrium is a question which has been thrown back and forth by investigators for at least three centuries. Here, for the first time, is a complete explanation of the true state of affairs in the fetal heart of one species of animals.

The first chapter of the monograph is an historical account divided into several periods. Much has been done to clarify certain misstatements which have been passed from one author to another in the literature. The second chapter of the book takes up the operative procedure and the special technique used to obtain roentgen cinematographic records. A detailed description is given of the special roentgenographic technique which was used to record the passage of contrast material through the heart and great vessels of the living fetus. Two types of recordings were used. In one of them a series of roentgenographic exposures was made on film 5 inches wide at the rate of three or four frames per second. The clearest images were produced by this method, but another, indirect method was found useful for obtaining records on 16 mm. motion picture film; an image on a fluorescent screen was photographed through a very fast lens.

The rest of the second chapter is devoted to a description of the results obtained by these methods—the actual course of the blood flow in the fetal lamb. Beautiful roentgenograms illustrate successive stages of the passage of radiopaque material through the vessels and heart in an adult animal (cat) and in the sheep fetus. In some experiments the contrast material reached the heart through the superior vena cava, and in others through the umbilical vein, ductus venosus, and inferior vena cava. The painstaking and detailed experiments which are described in this chapter of the book cannot be adequately covered in a review. One must read the authors' own account of these, and examine carefully their illustrations to fully appreciate the splendid results.

To summarize very briefly, they found that radiopaque material introduced through the superior caval stream passed through the right atrium, the right ventricle of the heart without traversing the foramen ovale, and entered the pulmonary trunk. A very appreciable amount went through the pulmonary circulation, and the rest of it was shunted by the ductus arteriosus into the descending aorta. Other experiments were performed to identify the ductus arteriosus definitely and to study the changes in the flow from the superior vena cava when the ductus arteriosus closed.

In an equally striking manner the authors demonstrated the course of radiopaque material traversing the inferior vena cava from the umbilical vein. It was found to pass very largely through the foramen ovale into the left atrium of the heart, the left ventricle, and thence through the arch of the aorta and the vessels to the heart itself, the upper extremities, and the head. A small fraction of the inferior caval stream traversed the right side of the heart, and thence went through the pulmonary circulation and ductus arteriosus.

Chapters III to VI are concerned with an attempt to tell the full anatomic and physiologic story of the cardiovascular system and circulation of the blood in the

tion, which has the advantages of purity, stability, and accuracy as to dosage and therapeutic effect.

The average oral digitalizing dose is 12⅔ mg. (thirty-eight tablets) while the oral maintenance dose was found to be ⅓ mg. (one tablet) in all but one case, which required ⅔ mg. (two tablets).

Digilanid intravenously in doses of 4 c.c. (2⅔ mg.) proves to be a potent therapeutic agent in congestive heart diseases with either normal rhythm or auricular fibrillation. The intravenous administration in doses of 4 c.c. is particularly indicated in cases of emergency, since its effect is reached within three hours, thus saving time of hospitalization.

AUTHOR.

Pines, I., Sanabria, A., and Arriens, R. T.: Mercurial Diuretics; The Addition of Magnesium Sulphate to Prevent the Toxic Effects of Their Intravenous Administration. Brit. Heart J. 6: 197, 1944.

The course of acute intoxication produced by the intravenous or intracardiac injections of esidrone was studied on normal dogs with the help of the electrocardiograph. It is concluded in agreement with other authors that mercurial diuretics in certain doses are general depressants for the whole cardiac muscle. The following pattern of intoxication was observed: changes of T waves, intraventricular and auriculo-ventricular conduction disturbances, diminution of frequency of impulse formation in S-A node, ventriuclar paroxysmal tachycardia, chaotic heart action, ventricular fibrillation, and death.

Tho addition of small quantities of magnesium sulfate (0.5 c.c. of a 20 per cent solution) prevents ventricular fibrillation and death, even if doses seven times higher than normal lethal doses are used. Magnesium sulfate, however, does not prevent, and even perhaps increases, the conduction disturbances resulting from the administration of lethal doses of mercurial diuretics. On the other hand, such amounts of magnesium sulfate increase the diuretic response, are entirely safe, and mix with mercurial diuretics without forming any precipitate.

It is suggested that small quantities of magnesium sulfate be incorporated into the mercurial diuretics in order to prevent fatal reactions resulting sometimes from the intravenous injections of these drugs.

AUTHOR.

Prescott, F.: Clinical Evaluation of the Pressor Activity of Methedrine, Neosynephrine, Paredrine, and Pholedrine. Brit. Heart J. 6: 214, 1944.

Tho clinical effectiveness of four pressor drugs, methedrine (pervitin, *d*-desoxyephedrine), paredrine, neosynephrin, and pholedrine (veritol, paredrinol) has been examined. Each drug was tested on twenty patients showing a severe fall in blood pressure (to 80 mm. Hg, systolic pressure, or to 10 mm. Hg, pulse pressure) during major surgical operations. The following were evaluated for each drug: optimum dose for a pressor response; maximum systolic and diastolic blood pressures, and rise in systolic and pulse pressuer after giving the drug; effect on pulse rate; time taken for the drug to act; duration of action; and side effects on the cardiovascular system. On the basis of the results obtained the clinical effectiveness of the four pressor drugs examined is in this order: methedrine, paredrine, neosynephrin, pholedrine. The principal criteria on which this opinion is based are: rise of systolic and pulse pressure when the drugs are given to surgical patients with a systolic blood pressure of 80 mm. Hg or less, the speed and duration of action, and the relative freedom from side effects on the cardiovascular system.

The table below summarizes the results obtained.

	Methedrine	Paredrine	Neosynephrin	Pholedrine
Satisfactory result	18	8	7	4
Unsatisfactory result	2	12	13	16
	20	20	20	20

A result was rated as satisfactory if the systolic pressure remained above 100 mm. Hg and the pulse pressure was not less than 30 mg. Hg for a period of two hours or more.

AUTHORS.

American Heart Association, Inc.

1790 Broadway at 58th Street, New York, N. Y.

The American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The American Heart Journal is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

Annual membership is $5.00. Journal membership at $11.00 includes a year's subscription to the American Heart Journal (January-December) and annual membership in the Association. The Journal alone is $10.00 per year.

The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

mature sheep fetus and the changes which occur during and after birth. Chapters VII and VIII deal with comparative anatomic and physiologic studies.

In the latter part of the book there are several chapters dealing with the cardiovascular system and changes occurring at human birth. Here the authors have brought together many widely scattered observations and have presented them in a most readable fashion.

The Foetal Circulation will be read with great interest by all who are concerned with the structure and function of the heart. It was a welcome surprise to learn of the publication of this book on a subject truly unrelated to the war, and in a country which has suffered so grievously in the present conflict. No small commendation to those responsible.

WILLIAM F. WINDLE.

EL APARATO CARDIOVASCULAR EN LAS INSUFICIENCIAS TIROIDEAS: By Dr. J. C. Mussio Fournier, Dr. José M. Cerviño, and Dr. Juan J. Bazzano. Salvat Editores, Barcelona and Buenos Aires, 1944, 150 pages, 27 illustrations.

This volume is published by the Institute of Endocrinology of the School of Medicine of Montevideo. The authors give a very complete review of the literature, together with the results of their study of sixty cases of myxedema.

Atherosclerosis, chronic renal lesions, myxedema heart disease, cardiac failure, angina pectoris, and myxedematous hydrops are discussed in the first part of the book as cardiovascular conditions which are directly due to myxedema.

The second part includes a discussion of cardiovascular disturbances caused by myxedema but superimposed on pre-existing lesions.

In the third part of the book there is a discussion of the transitory amelioration of either angina pectoris or cardiac failure which results from surgical removal of the thyroid gland.

In the last part the cardiovascular disturbances caused by thyroid treatment of myxedematous patients are considered.

The symptomatology of myxedema is studied systematically. Dyspnea, palpitation, precordial pain, mild peripheral edema, cyanosis, changes in cardiac rhythm and in arterial and venous pressure, and weakening of the heart sounds are critically considered. The two paragraphs on roentgenologic and electrocardiographic changes are of particular interest. The theory which attributes low voltage of the P and T waves to a change in the electrical resistance of the skin and that which attributes low voltage of QRS to the presence of fluid in the pericardial sac are discussed and held to be valid only in individual cases. Changes in the T wave and S-T segment can be ascribed directly to myxedema only when they fail to be modified by vasodilators and disappear during thyroid treatment.

Interstitial edema, in addition to separation and destruction of the myocardial fibers, is thought to be the main cause of the different signs of myocardial disease. Angina pectoris of myxedema which disappears after thyroid treatment is rare. It is attributed to underlying, silent coronary sclerosis, with superimposed functional elements either caused or favored by myxedema.

The discussion of the results of therapeutic thyroidectomy in cases of heart disease will be of interest to many cardiologists.

The photographs, roentgenograms, and electrocardiograms are well chosen and well reproduced, and the bibliography is complete.

A summary, with a brief statement of the authors' views on the different aspects of the subject, would have increased the value of the book, which will undoubtedly be read with interest.

ALDO LUISADA.

Announcement

In compliance with the order of the War Production Board, which limits the amount of paper consumed in the production of this JOURNAL, the publishers find it necessary to change the format. As soon as these restrictions are lifted the original format will be restored. Even though the number of pages has been reduced, the actual content of the JOURNAL has not been decreased to any appreciable extent.

THE EDITORS.

cases showed a surprisingly high incidence of both the acute and subacute varieties of bacterial endocarditis. The acute endocarditis group, comprising nine cases, has already been reported.[8] This communication is devoted to eighteen cases of subacute bacterial endocarditis in patients ranging from 60 to 87 years of age, which were observed on the wards of the Mt. Sinai Hospital during the past ten years. The age of 60 has been chosen as a minimum, partly because it is a convenient point of reference and partly because it represents a period of life when the aging process is usually well developed, having had its inception long before this.

The cases have been classified clinically according to the diagnostic problem involved, as follows:

Group A. Individuals presenting the typical, though often modified, clinical picture (nine cases).

Group B. Individuals in whom the diagnosis presents serious difficulties.
1. The bacteria-free cases (five cases).
2. Cases in which the diagnosis was completely obscured (four cases).

Tables I, II, and III summarize the salient clinical and pathologic features of these groups.

THE AGING OF THE CARDIOVASCULAR SYSTEM

The viewpoint of the ancients—that old age itself is a disease *(senectus ipsa est morbus)*—dominated medical thinking until about one hundred years ago, when, with increased knowledge, it became possible to differentiate many of the diseases that occur in advanced life. Today, the aging process and its inevitable end point, death, are considered essential properties of all living matter, and we can enumerate many of the fundamental structural and functional changes that characterize senescence. This has recently been well done by Carlson:[9]

> "Progressive age changes not as yet shown to be due to specific diseases are: gradual tissue desiccation; gradual retardation of cell division, capacity of cell growth and tissue repair; gradual retardation in the rate of tissue oxidation; cellular atrophy, degeneration, increased cell pigmentation and fatty infiltration; gradual decrease in tissue elasticity and degenerative changes in the elastic connective tissue; decreased speed, strength and endurance of skeletal muscle; and progressive degeneration and atrophy of the nervous system; impaired vision, hearing, attention, memory and mental endurance."

While theoretically possible, death from old-age changes alone rarely, if ever, occurs. Death is always found to be the immediate result of some definite process.

In considering aging of the cardiovascular system we find that Cohn[10] has carefully described the gross and microscopic anatomic changes in the heart as well as its functional alterations. It is, however, clear from clinical experience that these changes, as Boas[11] emphasized, do not produce a clear-cut clinical picture, nor do they of themselves bring about a fatal issue. Actually the hearts of old people often show remarkably good functional capacity in spite of organic handicaps. This has been attested by Willius'[12] study of the hearts of seven hundred patients 75 years of age and older.

Arteriosclerosis was at one time regarded as an invariable concomitant, if not an essential part, of the aging process. That this is not true can be seen in any post-mortem room where the aged come to examination. The gross

American Heart Journal

Vol. 29 | June, 1945 | No. 6

Original Communications

SUBACUTE BACTERIAL ENDOCARDITIS IN THE AGED

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INTRODUCTION

Subacute bacterial endocarditis has actively engaged the attention of medical investigators ever since the clinical and pathologic studies of Osler,[1] Horder,[2] Billings,[3] Schottmueller,[4] and Libman and Celler,[5] taught physicians to differentiate the disease from other cardiac afflictions. Today, interest in this condition has been stimulated by the dramatic results achieved by Touroff[6] in the surgical treatment of patent ductus arteriosus complicated by bacterial endocarditis and by the remarkable success of Loewe and his collaborators[7] in the treatment of the disease with large doses of penicillin in combination with heparin. The present contribution is concerned with the occurrence of the disease in advanced age, hitherto but little emphasized, and attempts to define the clinical picture as modified by the manifestations of senescence and by various associated diseases. That bedside studies of old-age changes and the related maladies must be undertaken in terms of present day medicine has been emphasized elsewhere.[8] The need is urgent since the number of older individuals in the population is increasing so rapidly that the practitioner is more and more confronted by medical and surgical problems directly related to the advancing years.

My attention was first drawn to the problem of subacute bacterial endocarditis in the aged some fourteen years ago by a patient, 84 years of age, whose only symptoms were persistent severe backache and low-grade fever. More than a month passed before the possible value of a blood culture was realized. The recovery of *Streptococcus viridans* from the blood stream, on several occasions, made the diagnosis clear. The cardiac examination disclosed coarse systolic murmurs at the apex and at the base of the heart. Petechiae were noted only twice during the three months that he was under observation. Chills and night sweats became troublesome late in the illness, which terminated with signs pointing to cerebral embolism. Necropsy was not performed. Discussion of the case with colleagues at the time indicated that subacute bacterial endocarditis in the aged was not rare in their experience. Indeed, it appeared that more than one personage of note had fallen victim to this disease late in life.

Interest in the problem was re-awakened by the recent review of seven hundred post-mortem examinations of individuals 60 years old and over. These

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From the Medical Services and the Laboratories, Mt. Sinai Hospital, New York City.
Received for publication Aug. 11, 1944.

TABLE I. CASES PRESENTING TYPICAL CLINICAL PICTURE

CASE	AGE (YRS.)	SEX	PREVIOUS RHEUMATIC HISTORY	BLOOD CULTURE	SIGNS OF VALVULAR DISEASE	EMBOLIC PHENOMENA	RENAL DISEASE	CLINICAL DIAGNOSIS	NECROPSY FINDINGS	MISCELLANEOUS FEATURES
1	60	F	14 years	*Enterococcus*	Mitral and aortic stenosis	Many petechiae, spleen palpable	Urine—red cells and albumin. Urea nitrogen, 16 mg.%	S.B.E.*	S.B.E. mitral valve with vegetation partially occluding orifice; rheumatic valvular disease, mitral and aortic stenosis, healed tricuspid valvulitis; focal embolic glomerulonephritis	Terminal clinical picture of extreme peripheral cyanosis and coldness suggested ball-thrombus of mitral valve
2	65	M	None	*Streptococcus viridans*	Systolic murmur at apex; diastolic murmur at left border of sternum	Embolic closure of right femoral artery, spleen palpable	Urine—albumin, red cells, casts. Urea nitrogen, 30 mg. %	S.B.E.	S.B.E. aortic valves mycotic aneurysm at base of aorta with fibrinous pericarditis. Syphilitic aortitis. Coronary artery sclerosis with marked narrowing of all branches. Multiple emboli in branches of inferior mesenteric artery	Wassermann reaction negative. No history of syphilis. Additional necropsy findings—healed duodenal ulcer, bilateral nephrolithiasis, marked diffuse arteriosclerosis
3	87	M	None	*Str. viridans*	Harsh systolic murmur at apex	Rare petechiae	Urine—albumin, no red cells	S.B.E.	S.B.E. mitral and aortic valves; moderate arteriosclerosis aortic and mitral valves; focal embolic glomerulonephritis; sclerosis of coronary arteries	Noteworthy are the age, the comparative well-being of patient for many weeks, and the minimal underlying arteriosclerotic changes in the valves
4	64	M	5 years	*H. parainfluenzae*	Harsh systolic murmur at apex	No petechiae. No clubbing of fingers	Urine—many red cells	S.B.E.	S.B.E. mitral valve and wall left auricle, rheumatic lesion mitral and tricuspid valves	Additional necropsy findings—*focal* embolic glomerulonephritis, left nephrolithiasis and chronic pyelonephritis

*S.B.E. = Subacute bacterial endocarditis.

diffuse vascular lesions commonly included in the term "arteriosclerosis" are conspicuously absent from the coronary arteries in as many as 30 per cent of old people.[13] Changes in the arteries properly ascribable to old age are to be correlated with those caused by mechanical, toxic, infectious, endocrine, metabolic, and neural agencies.

Since the association of increasing morbidity and mortality with advancing age is a commonplace of human experience which can be readily proved statistically,[14] we must look upon the structural and functional changes of senescence as providing the fertile soil, in which the most diverse diseases flourish singly and in combination with one another. So numerous are these morbid processes that the physician engaged in the treatment of old people finds it hard to differentiate clinically between so-called normal aging and its overgrowth of major maladies.

This difficulty will become clearer as we proceed with the study of subacute bacterial endocarditis, for here we shall see this disease flourish in association with many others. The question may well be posed: why do old people, who have had rheumatic heart disease for many years without symptoms, develop a secondary infection of the heart valves so late in life? Whether or not this lack of resistance to infection is to be regarded as an effect of the aging process is a problem that does not at present admit of ready solution.

LITERATURE

A review of the numerous papers on subacute bacterial endocarditis shows that nearly all the reported large series include cases in the higher age groups, but that, with several notable exceptions, no particular emphasis has been placed upon the older patients afflicted with the disease. In Blumer's[15] comprehensive review, published in 1923, he stated: "the figures indicate that subacute bacterial endocarditis is a disease of adolescents and young adults. In other words, the disease occurs during the period of greatest incidence of valvular heart disease, excluding the types due to syphilis and arteriosclerosis."

Clawson,[16] in 1924, reported 72 cases, of which nine occurred in the sixth decade, two in the seventh, and one in the eighth. Thayer,[17] in 1926, discussed 78 cases of which eleven occurred in the sixth and six in the seventh decade. Fulton and Levine,[18] in 1932, gave their findings in 111 patients, of whom the oldest was a man, 64 years of age. Hoff[19] in 1940, commenting on the clinical vagaries of endocarditis, described a group of five cases, characterized by progressive heart failure, which included a woman, 78 years of age; and a second group, characterized by a septic onset with symptoms of pneumonia and meningitis, of which one was a man, aged 60 years. Of thirteen patients, five were over 50 years of age.

Willius,[20] in 1940, presented the case of a man, aged 82 years, suffering from subacute bacterial endocarditis, and pointed out that the chief interest lay in the patient's age, since "in the vast majority of cases the patients are less than 50 years of age." The underlying valvular lesion was believed to be arteriosclerotic in nature.

In 1941, Christian,[21] in discussing the determinative background of the disease, emphasized the large number of young men affected, but took pains to point out that "subacute bacterial endocarditis cases occur in all age periods, and are not proportionately infrequent in the older groups, a fact that seems not to have been recognized very generally." Libman and Friedberg[22] in their monograph (1941) pointed out that "about two-thirds of the cases of subacute

Table II. Cases in the Bacteria-Free Stage

Case	Age (Yrs.)	Sex	Previous Rheumatic History	Blood Culture	Signs of Valvular Disease	Embolic Phenomena	Renal Disease	Clinical Diagnosis	Necropsy Findings	Miscellaneous Features
10	63	M	None	Sterile	Presystolic at apex; harsh systolic at apex and aortic area	Petechiae; clubbing of fingers; liver and spleen palpable	Urea nitrogen, 91 mg. %	Not made	S.B.E. aortic valve; mitral and aortic stenosis (rheumatic); chronic glomerulonephritis; coronary sclerosis with narrowing; left pyonephrosis with large calculus; cholelithiasis, choledocholithiasis, and hepatic lithiasis	Gradual onset with weakness and fever for 6 months before death. Death duo to right ventricular failure
11	64	F	Since childhood	3 cultures (3 weeks before death) sterile	Heart enlarged; long blowing systolic murmur over precordium; auricular fibrillation	No petechiae; marked hepatosplenomegaly	Urea nitrogen, (3 weeks before death), 50 mg. % Urine—fixed specific gravity; occasional red cells	Possibility of bacteria-free S.B.E. strongly considered. Hemoglobin, 42%; R.B.C. 2,500,000; W.B.C. 3,500 with normal differential	S.B.E. aortic and mitral valves with partial calcification of vegetations; chronic rheumatic heart disease, mitral, aortic, and tricuspid valves. Massive focal embolic glomerulonephritis	Four weeks before death observed in hospital for one week. Three weeks later readmitted with muscular twitching, emesis, epistaxis, and increased weakness. Died in twenty-four hours

5	60	M	None	*Str. viridans*	Systolic murmurs at apex and base. Transient auricular fibrillation	Rare petechiae. Spleen palpable	Urine—albumin and red cells; urea nitrogen, 21 mg. %	S.B.E. secondary to arteriosclerotic heart disease	--------------	Healed osteomyelitis of jaw; acute myocardial infarction 8 months before present illness. Not benefited by sulfonamides and hyperthermia
6	64	M	None	*Str. viridans*	Diastolic murmur at left border of sternum	Clubbing of fingers	Urine—many red cells	S.B.E. secondary to syphilitic heart disease	--------------	Wassermann and Kahn reactions positive; on admission productive cough, malodorous sputum led to bronchoscopic and lipiodol demonstration of lower lobe bronchiectasis
7	74	M	None	*Str. viridans*	Coarse systolic murmur all over precordium	Clubbing of fingers	Urine—red cells. Urea nitrogen, 17 mg. %	S.B.E. secondary to teriosclerotic valvular lesions	--------------	Fever and weight loss led to blood culture which was positive for *Str. viridans.* Sulfonamide therapy not tolerated
8	64	F	None	*Str. viridans*	Presystolic and systolic apical murmurs	Petechiae; spleen and liver palpable	Urine—albumin, casts, red cells. Urea nitrogen, 11 mg. %	S.B.E. secondary to rheumatic and arteriosclerotic heart disease	S.B.E. mitral valve; rheumatic valvular disease, mitral valve, bronchopneumonia, L.L.L., focal glomerulonephritis	X-ray of chest suggested mitral valve calcification. Electrocardiogram showed evidence of myocardial damage. Not benefited by sulfonamide therapy and hyperthermia
9	61	M	None	*Str. viridans*	Mitral and aortic insufficiency	Occluding petechiae; liver and spleen palpable. No clubbing	Urine—albumin and small numbers red cells. Urea nitrogen, 18 mg. %	S.B.E	Congenital septal defect with superimposed S.B.E. extending to right aortic cusp with perforation and to septal leaflet of tricuspid valve	Correct clinical diagnosis of S.B.E. but underlying cardiac defect not suspected, although apical heart sounds were obscured by murmur and phonocardiogram showed atypical group of murmurs

TABLE III. CASES IN WHICH DIAGNOSIS WAS COMPLETELY OBSCURED

CASE	AGE (YRS.)	SEX	PREVIOUS RHEUMATIC HISTORY	BLOOD CULTURE	SIGNS OF VALVULAR DISEASE	EMBOLIC PHENOMENA	RENAL DISEASE	CLINICAL DIAGNOSIS	NECROPSY FINDINGS	MISCELLANEOUS FEATURES
15	70	F	None	Not done	Cardiac enlargement; aortie diastolic murmur; B.P. 210/90; auricular flutter	No petechiae	Urea nitrogen, 41 mg. %	Graves' disease with secondary thyrotoxic heart disease and heart failure	S.B.E. mitral, aortic, and tricuspid valves; chronic rheumatic valvular disease, mitral, aortic, tricuspid; coronary artery sclerosis; multiple colloid adenomata of thyroid; focal embolic glomerulonephritis	Graves' disease, thyrotoxic and rheumatic heart disease obscured signs of endocarditis
16	62	F	None	Not done	Tachycardia, systolic murmur at apex and base	No petechiae, palpable spleen	Urine—albumin and casts	Right hemiplegia duo to cerebral hemorrhage	S.B.E. mitral valve; emboli, spleen, kidney, brain; acute fibrinous pericarditis; old occlusion right coronary artery; aneurysm left ventricle, acute myomalacia, myocardial fibrosis	That cause of hemiplegia was embolic was nover suspected. Persistent low-grade fever and palpablo spleen wero disregarded

12	74	M	None	Not done	Poor heart sounds; aortic diastolic murmur; congestion at lung bases; hepatic enlargement	Splenomegaly; no petechiae observed	Urine—much albumin; many red cells and white cells, with casts. Urea nitrogen, 37 mg. %; rose to 83 mg. %	Correct diagnosis not suspected	S.B.E. aortic valve with perforation of cusp; calcium in vegetations; chronic rheumatic valvular disease, mitral insufficiency; aortic stenosis	Correct diagnosis obscured by picture of renal insufficiency. Blood culture probably would have been sterile. Right ventricular failure important factor in fatal outcome
13	60	M	25 years	Not done	Cardiac enlargement; mitral and aortic lesions; congestive heart failure	No petechiae. Marked hepatosplenomegaly	Urea nitrogen, 58 mg. %; rose to 102 mg. %. marked anemia, hyperproteinemia	Rheumatic heart disease; chronic nephritis; cirrhosis of liver	S.B.E. aortic valve-perforation of cusp; rheumatic heart disease; mitral and aortic stenosis; glomerulonephritis, cirrhosis of liver	Advanced cardiac failure aggravated by anemia, and presence of uremia obscured signs pointing to S.B.E.
14	62	F	15 years	Sterile on three occasions	Cardiac enlargement; systolic murmur at apex and base; enlarged liver and spleen. Electrocardiogram indicated myocardial damage	Petechiae; clubbing of fingers	Urine, red blood cells. Urea nitrogen, 21 mg. %	S.B.E. in bacteria-free stage	--------------	Absence of renal insufficiency and anemia does not exclude S.B.E. in bacteria-free stage. Discharged unimproved

bacterial endocarditis occur in the third and fourth decades of life. Less commonly, however, the disease affects persons at any age of life from early childhood to old age.''

Two statistical studies on the age incidence of disease are of great interest. Hedley,[23] who studied rheumatic heart disease in Philadelphia, found, in the five-year period from Jan. 1, 1930, to Dec. 31, 1934, 288 fatal cases of subacute bacterial endocarditis, of which thirty, or 10.4 per cent, occurred in persons over 50 years of age. Of these, five patients, or 1.7 per cent of the total, were over 60 years of age. Of the thirty cases, fourteen were secondary to rheumatic heart disease, the remainder to other forms of cardiac disease. The author's only comment on these older patients is: ''all students of this problem with possible exception of Thayer observed that subacute bacterial endocarditis is infrequent during the age period under ten years and among persons over 60 years of age.''

Gelfman[24] has recently reported on the incidence of acute and subacute bacterial endocarditis in fatal rheumatic heart disease from two Boston hospitals. Of great significance for the student of the heart in old age is his finding that, of 452 cases of rheumatic heart disease, 78, or 17.3 per cent, occurred in patients 60 years old and over. Of the 452 patients, 115 or 25.4 per cent, suffered also from acute and subacute bacterial endocarditis. Of these 115 patients, eight, or 6.9 per cent, were over 60 years of age, five cases occurring in the seventh, two in the eighth and one in the ninth decade.

These statistical reports demonstrate that the recognized incidence of the disease in old age is considerable. It is probable, however, that many cases of subacute bacterial endocarditis escape recognition because of the difficulties in diagnosis and also because sick old people are not often sent to hospitals where the correct diagnosis may be disclosed at necropsy. An additional factor is the tendency on the part of physicians to ascribe all the complaints of old persons to some manifestation of arteriosclerosis.

That considerable confusion exists even among pathologists is indicated by Denman's analysis,[25] in 1942, of fifty autopsied cases of subacute bacterial endocarditis. Following the table of age incidence, which includes five cases in patients ranging from 51 to 60 years of age, Denman states: ''Six more cases were seen, but were excluded from this series because of their age and the possibility that their infections endocarditis was a terminal manifestation rather than the primary cause of death. Their ages were 59, 66, 67 (two), 75 and 78 years.''

The sole specific contribution to the problem of endocarditis in the aged has been made by Bayles and Lewis,[26] in 1940, who reported twenty-eight patients ranging from 40 to 72 years in age. The correct clinical diagnosis was made in only one-half of their cases. The most common pre-existing heart disease was rheumatic, occurring in 57 per cent, but arteriosclerotic, syphilitic, and congenital lesions (bicuspid aortic valves) were also present. They emphasize that the clinical features are essentially the same as in young patients but less accentuated: heart failure and azotemia are more common; demonstrable bacteriemia is less common. They conclude: ''Subacute bacterial endocarditis occurs more frequently than suspected or heretofore reported in older individuals.'' In addition they suggest that, if the lives of patients with rheumatic heart disease be prolonged by more efficient care, the complication of subacute bacterial endocarditis may be more frequently postponed to their later years.

17	62	M	None	Six cultures made of which only the fifth showed *Str. viridans*	Cardiac enlargement; systolic and diastolic murmurs at apex and base; electrocardiogram showed bundle branch block	Petechiae noted once; clubbing of fingers	Urine—red cells. Urea nitrogen rose from 25 mg. % to 37 mg. %	Arteriosclerotic heart disease; acute purulent parotitis	S.B.E. mitral and aortic valves with calcification; rheumatic valvular disease, aortic and mitral stenosis; bicuspid aortic valve; old incomplete occlusion of left coronary artery; aneurysm left ventricle. Diffuse arteriosclerosis	Arteriosclerotic heart disease, with complicating parotitis obscured correct diagnosis
18	62	M	None	Not done	Cardiac enlargement; systolic murmur at apex; B.P., 178/100	No petechiae	Urine—albumin and red cells	Possible gastrointestinal malignancy	S.B.E. mitral and aortic valves, wall of left auricle; chronic rheumatic valvular disease, mitral and aortic	Weight loss, rapid sedimentation rate and constipation led to suspicion of malignant gastrointestinal lesion. Ruled out after x-ray and sigmoidoscopy. Further investigation barred by sudden death after transfusion

be kept under observation throughout life, and a blood culture taken promptly if fever obscure in origin occurs." Uhley[33] has described Lutembacher's syndrome (interatrial septal defect and mitral stenosis) occurring in a man, aged 60 years, and mentions several other cases in older patients.[34]

In Case 9 of this series, a congenital defect of the interventricular septum *(maladie de Roger)* was found at necropsy. The patient was a 61-year-old man, who had no previous history of heart disease. Superimposed upon this typically located small defect were the lesions of subacute bacterial endocarditis, which had extended to involve and perforate the right aortic cusp and had also been implanted on the septal leaflet of the tricuspid valve. In Abbott's statistical analysis of 1,000 cases[32] of congenital heart disease, we find fifty cases of interventricular defect. The ages of the patients range from fetus to 49 years, and death is ascribed to bacterial endocarditis or endarteritis in thirteen cases.

Case 17 which exhibited a bicuspid aortic valve, is not included in the congenital group, since frank rheumatic lesions of the mitral valve were also present. Koletsky[35] has recently investigated the significance of bicuspid aortic valves in relation to bacterial endocarditis, confirming the views of Gross[36] that these valve changes are nearly all acquired and of rheumatic origin, and that this etiological factor explains their frequent association with superimposed endocarditis.

The mitral valve was involved by rheumatic changes in ten cases and by arteriosclerosis in two cases. Subacute bacterial endocarditis was engrafted on both arteriosclerotic valves, but only on eight of the ten rheumatic valves. The aortic valve was involved by rheumatism in eight cases, by syphilis in one case, and by arteriosclerosis in one case. Subacute bacterial endocarditis was found on the aortic valves ten times, in seven cases secondary to rheumatism and in one case each secondary to syphilis, to arteriosclerosis, and to congenital septal defect.

The aortic and mitral valves were simultaneously affected by rheumatic changes in eight cases, by arteriosclerotic changes in one case, and by subacute bacterial endocarditis in five cases. The tricuspid valve was the site of rheumatic changes in four cases, but of subacute bacterial endocarditis in only one of them. In Case 9 the tricuspid valve was secondarily involved by the vegetation arising in the interventricular septal defect.

As might be anticipated in a group of patients 60 years old and over, arteriosclerotic changes of marked degree were found in the hearts. Arteriosclerotic lesions of the valves were the site of vegetative endocarditis in only two instances (Cases 3 and 16). In four instances (Cases 2, 3, 10, and 15) marked coronary artery sclerosis was noted. In Case 16 the following changes were found: old occlusion of the right coronary artery, aneurysm of the left ventricle, acute myomalacia, and myocardial fibrosis; in Case 17, old incomplete occlusion of left coronary artery, and aneurysm of left ventricle. In this last case the clinical picture of subacute bacterial endocarditis was masked by the arteriosclerotic heart disease. In Case 16 the clinical picture was dominated by hemiplegia of embolic origin. In Case 14, not autopsied, the electrocardiogram indicated myocardial damage. Case 5 had suffered typical myocardial infarction six months before the diagnosis of endocarditis was made.

These findings indicate that even in old age rheumatic valvular lesions are the most important predisposing cause for localization of subacute endocardial inflammation. In our previous paper,[3] a similar conclusion was reached for acute bacterial endocarditis. Arteriosclerotic valvular lesions seem to be numerically less significant. On the other hand, arteriosclerosis of the coronary vessels

PATHOLOGY

Of the eighteen cases discussed in this paper, the fourteen which were examined at necropsy form the basis of the pathologic discussion. The principal etiological types of heart disease are represented in this group and furnish the foundation for the endocardial lesions. Congenital heart disease was present in one subject (Case 9), syphilitic in one (Case 2), thyrotoxic in one (Case 15), rheumatic in ten (Cases 1, 4, 8, 10, 11, 12, 13, 15, 17, and 18), and arteriosclerotic in seven (Cases 2, 3, 8, 10, 15, 16, and 17). Multiple etiological types were present in five of these cases: syphilis and arteriosclerosis occurring together in Case 2; rheumatic lesions and arteriosclerosis in Cases 8 and 10; and arteriosclerotic, rheumatic, and thyrotoxic changes in Case 15.

The incidence of clearly demonstrable old rheumatic valvular changes in ten of the fourteen autopsied cases is noteworthy in a group of patients over 60 years of age and is to be compared with Gelfman's Boston series.[24] Increasing emphasis by other writers shows that the occurrence of rheumatic heart disease in the aged must be regarded as considerable. White and Bland[27] have reported cases of rheumatic heart disease occurring in aged individuals. In the case of Rakov and Taylor,[28] a woman, 61 years old, was found at necropsy to have suffered from extensive acute rheumatic myocarditis, the entire myocardium being diffusely infiltrated by large numbers of Aschoff bodies. Attacks of paroxysmal nocturnal dyspnea, associated with congestive heart failure, were the outstanding clinical features in this case.

The occurrence of syphilis as an etiological agent in subacute endocarditis in the aged has been emphasized by Bayles and Lewis.[26] In Case 2, syphilitic aortitis and valvulitis were demonstrable at post-mortem examination, but for the true incidence in this series we must add Case 6, in which the diagnosis was well established on clinical grounds.

Some diversity of opinion exists as to the relationship of endocarditis to syphilitic aortitis and valvulitis. Smith,[29] reporting on the co-existence of syphilis of the aorta and bacterial endocarditis, presents two cases of acute and one of subacute endocarditis accompanied by syphilitic aortitis. In only one of these does he believe that the endocarditis was engrafted on a syphilitic valvulitis; in the second case the endocardial lesion occurred on undamaged valves, and, in the last, it was based on a rheumatic valvulitis. Boyd[30] believes that bacterial endocarditis superimposed on syphilitic valvulitis occurs more frequently than the literature would indicate. In 105 cases of bacterial endocarditis, he found fourteen to be definitely satisfactory examples of vegetative endocarditis superimposed on old syphilitic aortic valve disease. Koletsky[31] studied five cases with the diagnosis of cardiovascular syphilis and bacterial endocarditis. In four of these, stigmas of rheumatic fever were present, and in the fifth the endocarditis was engrafted on a normal aortic valve. My observations do not support the belief that syphilis is a significant predisposing factor in bacterial endocarditis.

The finding of congenital heart lesions in individuals who are advanced in years will not surprise anyone familiar with the work of Abbott.[32] The conditions described in her acyanotic and *cyanose tardive* groups are compatible with a fairly long life. In Touroff's series[6] of cases of patent ductus arteriosus complicated by subacute bacterial endocarditis, he reports two patients, one of 51 years, and the other 63 years. He points out: "Subacute bacterial endocarditis may occur at any age and constitutes a perpetual threat to the patient with a patent ductus arteriosus. . . . The patient with a patent ductus arteriosus should

in Case 2; and cerebral embolism in Case 16. In general, fewer infarctions were found in the bacteria-free group of cases.

BACTERIOLOGY

Of the nine cases classified as active (Group A), *Streptococcus viridans* was recovered from the blood stream in seven, *Enterococcus* and *Hemophilus parainfluenzae* in one each. Of the five bacteria-free cases (Group B, 1), blood cultures were not taken in two and in the others were repeatedly sterile. Of the clinically obscure cases (Group B, 2), blood cultures were not performed in three, and in the remaining case, six cultures were taken, of which only the fifth revealed *Str. viridans,* its source being erroneously ascribed to an acutely inflamed parotid gland.

In none of these cases was a mixed infection found, although in two of our series of acute bacterial endocarditis cases, two organisms were isolated from the blood stream. *Enterococcus* and *Staphylococcus albus* were associated in one patient; *Pneumococcus* and *Streptococcus hemolyticus* in the other. Libman and Friedberg[22] mention two types of mixed infection in subacute bacterial endocarditis. "The most common combination is an endocarditis due to an hemolytic streptococci with a secondary pneumococcus bacteremia, usually secondary to lobar pneumonia. We have observed also a secondary implantation of *Staphylococcus aureus* on valvular vegetations due to non-hemolytic streptococci." Orgain and Poston[42] have reported six patients with bacterial endocarditis from whose blood they repeatedly cultured two or more distinct species of bacteria. There was little in the history, physical examination, laboratory data, and clinical course of their cases to suggest a mixed infection. They emphasize that recognition of a mixed infection is of fundamental importance in sulfonamide therapy, since the drug may affect one organism and not the other.

The occurrence of *H. parainfluenzae* as the cause of subacute bacterial endocarditis is well known. Rose,[43] in a recent communication, has pointed out the bacteriologic differentiation between *H. influenzae* and *H parainfluenzae*, emphasizing the great rarity of the former in endocarditis. He contributes an authentic case of *H. influenzae,* Type A., endocarditis.

The portal of entry of the infection in subacute bacterial endocarditis is nearly always obscure, although the upper respiratory tract and the teeth are frequently implicated on the basis of clinical study. In this series of old people the associated and unrelated pathologic lesions may be of importance, such as the bilateral nephrolithiasis in Case 2, the healed (?) osteomyelitis of the jaw in Case 5, and the left pyonephrosis and biliary lithiasis in Case 10. That there is a specific lowering of resistance to bacterial infection attributable to the changes of senescence, can only be inferred from the occurrence of the valvular infection late in the life of individuals who had undoubtedly carried rheumatic valvular lesions throughout a large part of their lives. Other explanations of equal validity are possible.

CLINICAL FEATURES

Table IV gives the age and sex distribution of the eighteen cases. The male cases predominate over the female, and, while these figures can have but little significance, it will be recalled that in series of younger patients the disease also seems more prevalent among men. Thirteen of the cases occur in the first half of the seventh decade of life, one in the second half, three in the first half of the eighth decade, and one in the second half of the ninth. These figures

occurred in six of the thirteen cases, often associated with severe myocardial damage, and thus assumes importance by influencing the clinical picture, tending to obscure the presence of the endocarditis.

The cardiac lesions associated with sclerosis of the coronary vessels resulting in acute and chronic changes in the myocardium may have another pathogenic relationship to bacterial endocarditis. Keefer[37] has emphasized the occurrence of nonbacterial thrombotic endocarditis[38] in a variety of chronic diseases, including chronic heart disease, leucemia, cancer, and chronic pulmonary tuberculosis, and believes that these sterile platelet thrombi furnish favorable sites for the localization of bacteria. The experimental work of Nedzel[39] also has direct bearing on the pathogenesis of endocarditis in general and particularly in the aged. This worker studied, in dogs, the effect on the heart valves of pressor episodes artificially induced by injections of pitressin and found that by this method he could produce changes in the valvular endothelium and the subendothelial tissues which resembled, at first, nonbacterial and, later, bacterial endocarditis. He relates these artificial and highly exaggerated vascular spasms to those disturbances of splanchoperipheral balance occurring in human beings as the result of unusual changes in the meteorologic environment. The fundamental cause of the tissue changes, according to Nedzel, is local tissue anoxia of varying intensity. If these experimental studies are valid, they give us insight into the way in which nonbacterial thrombotic endocarditis may arise in a variety of serious diseases, and into the mechanism by which these primary lesions become secondarily infected.

In addition to the association of endocarditis with marked cardiac arteriosclerosis, certain other concomitant pathologic features of these cases are noteworthy. In Case 1 the terminal clinical picture of extreme peripheral cyanosis and coldness of the extremities suggested the diagnosis of ball-thrombus in the left auricle. Post-mortem examination revealed that the mitral valve vegetation was large enough to partially occlude the mitral orifice and had the same effect as a free ball-thrombus. In Case 2, where subacute bacterial endocarditis was engrafted on syphilitic aortitis and valvulitis, a mycotic aneurysm was present at the base of the aorta with an overlying fibrinous pericarditis. Multiple emboli were found in branches of the inferior mesenteric artery. In addition, a healed duodenal ulcer, bilateral nephrolithiasis, and chronic pyelonephritis were found. Case 10 revealed to the pathologist a left calculus pyonephrosis, cholelithiasis, choledocholithiasis, and hepatic lithiasis. Cirrhosis of the liver was an additional lesion in Case 3.

The associated renal lesions are worthy of separate consideration since this series shows, in striking fashion, the difference between the active and bacteria-free cases, as pointed out by Libman,[40] and Baehr and Lande.[41] Four of the six cases in Group A showed focal embolic glomerulonephritis without any clinical evidence of renal insufficiency, while two of the five bacteria-free cases showed chronic diffuse glomerulonephritis at post-mortem examination, associated with clinical signs of marked renal insufficiency and with increased urea nitrogen in the blood. Another case in this group disclosed renal insufficiency due to massive focal embolic glomerulonephritis.

Gross infarcts of the kidneys were noted in Cases 4, 11, 15, and 17. In the last case, the left adrenal gland was also involved by infarct. Among other embolic phenomena are noted multiple embolic abscesses of the myocardium, kidneys, spleen, and intestines in Case 1, mycotic aneurysm at base of aorta, multiple mycotic aneurysms of the superior mesenteric and right iliac arteries

the correct diagnosis was not always directly arrived at, partly because of misplaced clinical emphasis, and partly because the bedside observations did not at once fit into a diagnostic whole. The following case history is noteworthy because of the advanced age of the patient, the minimal underlying arteriosclerotic changes in the valves, the comparative well-being of the patient for many weeks, and the large numbers of bacteria in the blood stream at all times with minimal clinical manifestations.

CASE 3.—This 87-year-old physician had enjoyed good health except for prostatism. Five weeks before admission, malaise, chilly sensations, and fever were noted. Later, shaking chills occurred on several occasions. On examination he was found to be a thin, well-preserved, elderly man with a temperature of 102° F.; moderate general arteriosclerosis; heart, not enlarged, with a harsh systolic murmur at the apex; and liver enlarged 2 fingerbreadths below the costal margin. The hemoglobin was 85 per cent, and the white blood cell count was 14,000 with 80 per cent polymorphonuclears. The urine contained albumin but no red blood cells. An electrocardiogram showed left axis deviation, small Q_1, and slurred QRS. Repeated blood cultures showed *Str. viridans* in all flasks. Only rarely were petechiae found.

Sulfapyridine had no effect on the bacteriemia, and other methods of therapy, such as hyporthermia, seemed too strenuous to attempt. The mild course of this infection in the early stages was very striking. The patient was frequently able to be out of bed, particularly in the morning, and outwardly looked remarkably well. He died four and one-half months after onset.

On post-mortem examination (Montefiore Hospital) the following findings were established: mild arteriosclerosis of mitral and aortic valves, with superimposed bacterial endocarditis; infarctions of spleen and kidneys; focal embolic glomerulonephritis; arteriosclerosis of coronary arteries, general arteriosclerosis; chronic cholecystitis and cholelithiasis; benign hypertrophy of prostate.

The confusion caused by presenting symptoms pointing to either a suppurative or neoplastic lung lesion is well illustrated in an elderly man suffering from syphilitic aortitis. Notable in this case were the absence of splenic enlargement and of embolic phenomena except red blood cells in the urine, the well-marked euphoria (*Spes endocarditica* of Horder), and the progressive change in the patient's facies to a well-defined *café-au-lait* coloration.

CASE 6.—For six weeks this 64-year-old butcher suffered from cough, productive of one cupful of malodorous sputum daily, and had lost 22 pounds in four months. There was no history of syphilis or rheumatic fever. On examination he was pale, his pupils were irregular, but reacted to light; and his heart showed a diastolic murmur audible at left border of sternum. Blood pressure was 150/60. Moderate clubbing of the fingers was noted. The hemoglobin was 60 per cent, and the white blood cell count was 16,000 with 76 per cent polymorphonuclears. The Wassermann and Kahn reactions were strongly positive. Roentgen examination of the chest showed an infiltration near the right border of the heart. Lipiodol demonstrated a cylindrical dilatation of right lower lobe bronchus.

On admission, the general diagnostic opinion favored either a suppurative bronchopneumonia or a pulmonary neoplasm. Two bronchoscopic examinations failed to give confirmation to these views, and also failed to account for the daily rise in temperature up to 102° F. at night. Only then were all the facts correlated; namely the fever, anemia, microscopic hematuria, aortic insufficiency, and early clubbing of the fingers. Blood culture, when finally taken, revealed a *Str. viridans* bacteremia. The patient was discharged to the care of his own physician nine weeks after admission. He died, at home, two weeks later. Necropsy was not performed.

THE BACTERIA-FREE CASES (GROUP B, 1)

To Libman[10] we owe the description of the "cases of subacute bacterial endocarditis that have spontaneously become bacteria-free." He has emphasized that the clinical picture of this phase of the disease is due to damage to the kidneys and the blood-forming organs during the bacterial stage and to embolism

TABLE IV. DISTRIBUTION OF CASES ACCORDING TO AGE AND SEX

AGE (YRS.)	MALE	FEMALE
60 to 64	7	6
65 to 69	1	–
70 to 74	2	1
75 to 79	–	–
80 to 84	–	–
85 to 89	1	–
Total	11	7

may be compared with those cited from other sources in our review of the literature.

The eighteen cases herewith reported have been separated into three groups on the basis of the clinical pictures presented and the difficulties each group places in the way of correct diagnosis. In the first group of nine cases the clinical diagnosis presented only moderate difficulty and was confirmed in the six cases which came to autopsy. In the second group of five cases the correct diagnosis was made clinically in only two, and of the third group of four cases none was interpreted correctly. Of the total eighteen cases the clinical diagnosis was made correctly in eleven, or 61 per cent. In the Bayles and Lewis series of twenty-eight individuals over 40 years of age, one-half received the correct diagnosis ante mortem.

THE TYPICAL, BUT OFTEN MODIFIED, CLINICAL PICTURE (GROUP A)

Libman and Friedberg[22] list the four following features in combination as leading to the diagnosis of subacute bacterial endocarditis: "(a) a valvular defect or a congenital lesion, (b) a febrile course, (c) embolic phenomena, and (d) a positive blood culture." These criteria are amply satisfied by the cases in Group A, but certain features will be pointed out which tend to modify the typical clinical picture and to make the diagnosis difficult at times. Prerequisite to diagnostic accuracy is the knowledge that subacute bacterial endocarditis may occur in the aged, and the clinician must fit his observations into a line of thought that suggests the value of taking a blood culture. In my first case, mentioned briefly in the introduction, a whole month passed before the value of this procedure occurred to me. In old people cardiac murmurs are common, and are customarily dismissed as "arteriosclerotic," although careful study is often required to establish their true cause and significance. Fever in old persons is not uncommonly of low-grade intensity, and, if not overlooked entirely, is apt to be explained away as due to a "patch of bronchopneumonia" or to an infection of the urinary tract.

Study of the clinical records of the nine cases in Group A shows that all had heart murmurs, although some were incorrectly interpreted, as in Case 9. All but one had red blood cells in the urine, many showed albuminuria, but none had evidence of renal insufficiency. Petechiae were abundant in two persons, rare in three persons, and not observed in four. Fever was regularly present in these patients, even in the man 87 years of age (Case 3). Clubbing of the fingers was noted in two cases. The spleen was palpable in five cases, the liver in four. Anemia was present in only four of these cases. All had positive blood cultures, seven showing *Str. viridans,* and one each, *Enterococcus* and *H. parainfluenzae,* but positive cultures were not always obtained on the first attempt.

In retrospect one finds that each of these cases conformed to Libman's four diagnostic criteria. Study of typical case histories will indicate, however, that

termination could be drawn. Diagnostic discussion leaned to bacteria-free subacute bacterial endocarditis, based on the cardiac findings, the anemia, the splenomegaly, and the symptoms of uremia.

Post-mortem examination disclosed: healing subacute bacterial endocarditis with calcification of vegetations, involving aortic and mitral valves; chronic rheumatic valvular disease, tricuspid, mitral, and aortic valves; focal embolic glomerulonephritis and diffuse glomerulonephritis; marked splenomegaly.

In Case 12 the clinical picture of endocarditis is obscured by the renal insufficiency. The necropsy findings lead one to conclude that the blood culture, had it been done, would have proved sterile.

History was elicited with difficulty from this 74-year-old man. In past year he had suffered from a moderate cough, dyspnea on exertion, and urinary urgency and frequency; just before admission hematuria and melena were observed. On examination he was found febrile, cyanotic, dyspneic, with heart sounds distant, and an aortic diastolic murmur audible. The blood pressure was 126/150. There was congestion at both lung bases; enlarged liver, spleen, and prostate; and general peripheral sclerosis. The hemoglobin was 60 per cent, and the white blood cell count was 8,000, with 60 per cent polymorphonuclears. Urine contained large amounts of albumin, occasional hyaline and granular casts, and frequent red and white blood cells. Urea nitrogen was 37 mg. per cent. Electrocardiogram showed regular sinus rhythm, frequent ventricular extrasystoles, QRS moderately low, and P waves low. Urea nitrogen rose gradually to 83 mg., and the patient died ten days after admission, in uremia. Blood culture was not done, as the true diagnosis was at no time suspected.

Post-mortem examination showed the following: subacute bacterial endocarditis (bacteria-free) of the aortic valve with perforation of the right anterior cusp; chronic rheumatic valvular disease, mitral insufficiency; aortic stenosis and insufficiency; infarct of the spleen; focal embolic glomerulonephritis and chronic diffuse glomerulonephritis; general arteriosclerosis; coronary arteriosclerosis with narrowing; and fibroadenoma of the prostate.

THE COMPLETELY OBSCURE CASES (GROUP B, 2)

The four cases, which have been included in Group B, 2 as completely obscure, clinically, exemplify vividly the varied ways in which the diagnosis may be missed. In the bacteria-free cases renal insufficiency proved the greatest stumbling block. Here, in order, we find congestive heart failure due to rheumatic and thyrotoxic heart disease, hemiplegia of unsuspected embolic origin (Case 16), chronic valvular disease in association with acute parotitis (Case 17), and a mistaken diagnosis of gastrointestinal malignancy (Case 18), leading the clinician astray. Of the four cases, three are in the active phase and the fourth is in the bacteria-free stage, although no blood cultures were taken in any of them.

Libman and Friedberg state that the fatigability, weakness, sweating weight loss, nervous symptoms, and the elevated basal metabolic rate of subacute endocarditis may simulate Graves' disease, but they also warn that a patient with Graves' disease may develop subacute endocarditis. Hoff[19] has reported a man, 55 years of age, suffering from subacute bacterial endocarditis with splenomegaly and anemia. Within one year of death, his disease had been diagnosed as toxic goiter. Thyroidectomy was performed a year previously, and again, four months before death. He had been given two courses of deep roentgen therapy, the last one immediately before admission to the hospital.

In Case 15 we find a woman, aged 70 years, who had a symptomless goiter for twenty years. For one year year loss of weight, easy fatigue, polyphagia, elevated basal metabolic rate, dyspnea, orthopnea, and edema of the legs had been noted. The clinical picture was that of congestive heart failure due to Graves' disease. At post-mortem examination subacute bacterial endocarditis of the tricuspid, mitral, and aortic valves was a surprising finding, as was the

due to the fibrous and calcified vegetations resulting from the healing process. For a fatal case to be considered in the bacteria-free stage, the vegetations must be shown by spreads and sections to contain no bacteria. The mere absence of bacteria from the blood stream, even after repeated attempts at culture, is not enough to show that the heart valves are free of infection, since this may also occur from time to time in the active cases. In establishing the clinical diagnosis, Libman emphasized the following features in association with chronic valvular disease: renal insufficiency, severe progressive anemia, emboli, striking splenomegaly, and brown pigmentation of the face. Keefer[44] has stressed the fact that 20 to 25 per cent of all cases, as proved by post-mortem examination, belong in the group without bacteriemia. He distinguished five classes: (a) patients with right-sided valvular disease, multiple pulmonary infarcts, and jaundice; (b) patients with renal insufficiency; (c) patients with heart failure; (d) patients with splenomegaly and anemia; and (e) patients with hemiplegia. He considers renal insufficiency as the most important clinical difference between these cases and those with positive blood cultures.

Five cases in this series have been classified as belonging in the bacteria-free group. Two of these (Cases 11 and 14) were diagnosed correctly before death. In Case 10 the clinical picture was dominated by long-standing rheumatic valvular disease, cardiac failure, and renal insufficiency. In Case 12 renal insufficiency again obscured the real significance of the symptoms. In Case 13 cardiac failure combined with hepatic cirrhosis seemed an adequate explanation of the clinical findings.

Regarding the details of the clinical picture we note that two patients were males, three were females, and the age range was from 60 to 74 years. Fever was present in one case, and in only one was a change in facial color noted. Clubbing of the fingers was present in two cases, and petechiae were observed in two cases. Heart failure was present in three cases, but arrhythmia occurred in only one; the liver and spleen were enlarged and palpable in all five cases. Anemia was present in three cases; renal insufficiency in four. Blood cultures were taken in three cases and showed no growth, even on repeated attempts. In the other two cases blood cultures were not done because there seemed to be no clinical indications.

At necropsy, bacteria were not present in the valve crushings. In two cases the vegetations contained deposits of calcium. The occurrence of chronic glomerulonephritis has already been emphasized in the section devoted to pathology. The following case histories will clarify the problems posed by the bacteria-free group. Case 11 presents the classical features of the bacteria-free stage, as described by Libman, especially the death in uremia, associated with congestive heart failure and auricular fibrillation:

For many years this 64-year-old woman had suffered from rheumatic heart disease. She was re-admitted because of increasing weakness, epistaxes, nausea, and emesis. When seen some weeks before, fixation of specific gravity of urine and moderate nitrogen retention in the blood had been noted. On admission examination marked asthenia and muscular twitchings of the upper extremities were noted; linear hemorrhages were found in the fundus oculi; dullness was present at both lung bases with râles at the right base; the heart was enlarged to the left; the sounds were of fair quality; a long blowing systolic murmur was heard over the precordium, maximal at base and propagated toward vessels of the neck, with a thrill at the base; the rhythm was totally irregular. The blood pressure was 130/60. The spleen was enlarged to the umbilicus, and the liver edge was felt 4 cm. below the costal margin. No petechiae were observed. The hemoglobin was 42 per cent; the red blood cell count was 2,500,000; and the white blood cell count was 3,500, with a normal differential count. Unfortunately the patient died within twenty-four hours before blood for urea nitrogen de-

found at onset of parotitis, its origin from the heart valves was doubted. The electrocardiogram originally showed left bundle branch block with left ventricular hypertrophy and marked myocardial damage, but no progression was seen in subsequent tracings. The patient became abruptly worse during his eighth week in the hospital; his urea nitrogen mounted to 70 mg. per cent; he vomited repeatedly, became dehydrated, and died. Post-mortem examination disclosed subacute bacterial endocarditis (healing) of the mitral and aortic valve; aneurysm of the mitral valve, two dissecting aneurysms of the aortic valve; splenic, renal, and left adrenal infarctions; rheumatic heart disease, mitral and aortic insufficiency and stenosis; bicuspid aortic valve, etiology (?); old occlusion, incomplete, of anterior descending branch of the left coronary artery; aneurysm of the apex of the left ventricle and inferior anterior one-third of septum; arteriosclerosis of the aorta, coronary arteries, and pulmonary arteries; chronic cholelithiasis and cholecystitis; fibro-adenoma of the prostate.

In Case 18, fever, anemia, heart disease, and microscopic hematuria were shown clinically, which, viewed in retrospect, should have led to clinical suspicion of the true state of affairs. Weight loss and constipation prompted the search for a malignant tumor of the gastrointestinal tract.

Two years previously, this 62-year-old man first learned that he was suffering from hypertension and cardiac hypertrophy. For the preceding few months increasing weakness and weight loss were noted, with occasional nocturnal dyspnea. He appeared pale and chronically ill; the heart was markedly enlarged with an apical systolic murmur and snapping first sound. The blood pressure was 178/100. The hemoglobin was 62 per cent; the white blood cell count was 15,750, with 57 per cent segmented polynuclears, 32 per cent nonsegmented, 4 per cent lymphocytes, and 7 per cent monocytes. The urine showed a faint trace of albumin and a moderate number of red cells. The electrocardiogram showed slight slurring of the QRS complex.

Because of weight loss, constipation, and rapid sedimentation rate, a gastrointestinal malignancy was at first suspected. Sigmoidoscopy and barium enema showed no abnormality. Renal studies were planned because of hematuria, but whole blood transfusion was considered a necessary preliminary. The patient died in pulmonary edema thirty minutes after the transfusion.

Post-mortem examination surprisingly disclosed: subacute bacterial endocarditis of the mitral and aortic valves and the wall of the left auricle; chronic rheumatic valvular disease, mitral and aortic valves, with calcification of mitral chordae tendineae; acute splenic tumor; hypertrophy of both ventricles; pulmonary edema and emphysema; and arteriosclerosis of the kidneys. Crushings of vegetations showed gram positive cocci abundantly.

The difficulties in diagnosis due to the latency of the endocarditis have been strongly emphasized by Musser.[17] He cites a man, 50 years of age, who died as the result of congestive heart failure and bilateral brachial emboli. The post-mortem finding of subacute bacterial endocarditis was entirely unsuspected. A recent case record[48] from the Massachusetts General Hospital deals with a woman, 54 years of age, who showed, on admission, arteriosclerosis, diastolic hypertension (184/110) and hepatomegaly. She was operated upon to relieve uterine prolapse. Vaginal hysterectomy and perineorrhaphy under gas-ether anesthesia were performed. The operation lasted three hours, and toward its close a sharp drop in blood pressure was noted. The patient died twenty-four hours later. The clinical diagnosis was a cerebral vascular accident. At post-mortem examination an embolus was found in the left middle cerebral artery, but its source was subacute bacterial endocarditis of the mitral valve superimposed on chronic rheumatic valvular disease, mitral stenosis.

DIFFERENTIAL DIAGNOSIS

The preceding cases indicate the broad range of differential diagnosis required in establishing the presence of subacute bacterial endocarditis in the aged. Heart disease due to congenital lesions, rheumatic fever, or syphilis may be present in old people, and together with the commonly found triad of

disclosure of chronic rheumatic valvular disease of the tricuspid, mitral, and aortic valves. Focal embolic glomerulonephritis was present. In this patient the endocarditis is believed to be secondary to both rheumatic and thyrotoxic heart disease.

Case 16, which follows, served originally to crystallize the writer's interest in this phase of the problem, since the hemiplegia was thought by all to be of local vascular origin. No one for a moment considered that it might be embolic. The fever was likewise "explained away," and the enlarged spleen was not identified although easily palpable.

For thirteen years, this 62-year-old woman had hypertension with occasional vertigo and syncope. On the morning of admission to the Mt. Sinai Hospital, she was found with complete right hemiplegia, unable to speak. Blood pressure at home was 208/108. These findings were confirmed in the hospital, where the heart rate was regular but rapid; a systolic murmur at the apex and base was noted. A mass in the left upper quadrant was felt, and was described as large, hard, irregular, and immovable. The hemoglobin was 68 per cent; the red blood cell count was 4,380,000; and the white blood cell count was 21,000 with 81 per cent polymorphonuclears. The urine contained albumin, a few hyaline and granular casts, and a moderate amount of white blood cells.

The patient ran an irregularly febrile course during her stay in the hospital with temperature ranging between 99° and 103° F. It was assumed that the fever was due either to the cerebral vascular accident or some intra-abdominal inflammatory disease, as suggested by the left upper quadrant mass. She lost ground gradually and died eight days after admission.

Post-mortem examination disclosed subacute bacterial endocarditis of the anterior leaflet of the mitral valve; multiple emboli to the spleen and kidney; acute fibrinous pericarditis; old occlusion of the right coronary artery; and aneurysm of the left ventricle with acute myomalacia and myocardial fibrosis.

The involvement of the central nervous system in endocarditis has been discussed by Kernohan, Woltman, and Barnes.[45] These authors stress the occurrence of embolic lesions leading to hemiplegia, Jacksonian attacks, hemianopsia, aphasia, brain abscess, and meningitis. Toone[46] has emphasized that the basic brain pathology in endocarditis is an embolic meningo-encephalitis, and that these brain lesions frequently produce the outstanding clinical features of the syndrome.

In Case 17 every effort was made to establish the presence of a bacteriemia, but when one of six attempts showed *Str. viridans* it was attributed to an acute parotitis. In view of the evidences of healing found in vegetations at autopsy this interpretation may have been correct. The long period of hospital observation, eight weeks, is noteworthy.

Five months previously, this 62-year-old man suffered myocardial infarction necessitating two months' rest in bed. For three months before admission he had noted insomnia, asthenia, dyspnea on exertion, pallor, and a 20 pound loss in weight. During this period his physician observed development of systolic and diastolic murmurs audible at the base of the heart. At admission examination he was found to have one conjunctival petechia, cardiac enlargement, systolic and diastolic murmurs at both apex and base; blood pressure, 134/65; liver enlarged; spleen, firm edge, just palpable; clubbing of fingers. The hemoglobin was 52 per cent; red blood cell count was 4,000,000; and the white blood cell count was 5,200; with 60 per cent polymorphonuclears.

During the patient's first three weeks in the hospital, his fever ranged between normal and 101° F. Urine sediment showed red blood cells. Blood urea nitrogen rose from 25 to 37 mg. per cent. After six weeks in the hospital, acute left parotitis developed, responded to radiotherapy, and drained through the duct. Culture of pus yielded *Staph. albus, Staph. aureus, Enterococcus,* and *Str. hemolyticus.* In all, six blood cultures were made. All were negative except the fifth, from which *Str. viridans* was cultured in one flask. As this was

age from 60 to 87 years are analyzed, emphasizing the high incidence of rheumatic valvular lesions as the basis for the endocarditis, with the occurrence in this role less frequently and in the order named, of arteriosclerotic, syphilitic, congenital, and thyrotoxic heart disease.

By classifying the cases into two large groups according to the diagnostic problems presented, it has been possible to show that approximately one-half of the cases exhibit a typical, though often modified, clinical picture, and that the second group of more difficult cases may be further subdivided. In the first subdivision are placed the bacteria-free cases, characterized predominantly by heart failure, splenomegaly, anemia, and renal insufficiency. Into the second subdivision are placed the cases which completely elude precise diagnosis, due to the masking of the endocarditis by envolvement of the central nervous system and by a bewildering variety of other clinical findings which tend to distort diagnostic emphasis.

The multiplicity, chronicity, and duplicity of disease in the aged cannot be stressed too often. These cases of endocarditis show in striking fashion how this disease forms the *closing incident* of a long life during which time many maladies have been acquired and either overcome or endured. The writer believes that the difficulties of accurate differential diagnosis of disease in the aged, as exemplified in these case presentations, offer a stimulating challenge to the keen clinician. Diagnostic success holds out the hope of possible therapeutic achievement by using the newer methods of combating infections.

This study of subacute bacterial endocarditis in the aged demonstrates anew the inestimable value of clinical and pathologic correlations, along the lines laid down by Morgagni nearly two hundred years ago. In this modern day, it would hardly seem necessary to belabor the point, but for real progress in the diagnosis of disease in the aged, more old people must be studied by the pathologist as well as by the clinician. The general hospitals have a large responsibility as regards the acute medical and surgical problems of the aged, but vast fields of investigative endeavor lie open for the progressive homes for the aged where the clinicial material is largely made up of the chronic, insidious, and slowly progressive disorders of old age, and where the residents are under observation over long periods of time.

CONCLUSIONS

1. At the present time subacute bacterial endocarditis occurs in the aged more frequently than is generally realized. With the increase in the number of old people in the population, an increased incidence of this disease may be expected in the higher age groups.

2. Clinical recognition of subacute bacterial endocarditis depends upon the physician's constant effort to achieve diagnostic accuracy in the aged by utilizing for them the same careful observation and the same methods of precision commonly employed for the young.

3. The chief obstacle to diagnostic exactitude lies in the multiplicity of the pathologic processes in old people and in the difficulty of determining the relationship of these processes to the total clinical picture. In spite of close observation and study there will still remain a group of cases in which the subacute bacterial endocarditis will first be disclosed on the autopsy table. Additional clinical and pathologic investigations are needed to keep down the number of these post-mortem surprises.

coronary artery sclerosis, coronary artery thrombosis, and myocardial infarction, serve as the background for an endocarditis. Neurological complications, as well as renal insufficiency and signs such as weight loss and anemia, pointing to the presence of malignant tumors, may mask the disease. While the finding of a positive blood culture would seem to clarify diagnostic problems, there are occasions when the opposite occurs. Herrmann[49] has reported a series of such cases in younger individuals.

In the following case the presence of a heart murmur, petechiae, and a positive blood culture led to an incorrect clinical diagnosis of endocarditis.

A man, aged 55 years, who had suffered from diabetes for over twenty years, developed a gangrenous cellulitis of the right foot following an injury. Amputation was finally performed, although just before operation the patient suffered an attack of myocardial infarction, proved by electrocardiogram. Following operation he did well; the stump healed without sign of infection; he became afebrile and was allowed out of bed after one week. He was discharged and about to leave the hospital when, on the twenty-second day after amputation, his temperature rose suddenly to 104° F. The following day the temperature was 103.2° F. The twenty-third day it became normal and remained so for three days. On the twenty-ninth day postoperatively he had a chill which recurred on the thirtieth, thirty-third, and thirty-fifth postoperative days. Blood culture contained *Str. viridans*. Examination of the stump proved normal, but the femoral vein was ligated as a precaution. Sulfonamide therapy did not affect the blood stream infection. Petechiae and a heart murmur were now detected. The patient died ten weeks after admission as the result, it was thought, of subacute bacterial endocarditis. At post-mortem examination, the findings were: thrombosis of the left renal artery with suppurating infarct of the right kidney; severe coronary sclerosis with narrowing and recent thrombosis of the left circumflex branch; myomalacia of the posterior wall of the left ventricle with abscess in the papillary muscle.

TREATMENT

Excellent reviews of the results of treatment of subacute bacterial endocarditis prior to the introduction of the penicillin-heparin method have been contributed by Smith, Sauls, and Stone,[50] Lichtman,[51] and Eggleston.[52] In January, 1944, the startling report of the work of Loewe, Rosenblatt, Greene, and Russell[7] appeared, giving the details of the administration of heparin and penicillin and the case histories of seven consecutive patients who were successfully treated. Included among their more recent and unpublished successful cases are at least two individuals over 60 years of age.[53] It seems likely, therefore, that the improved therapeutic prospect will include older patients as well as the younger ones. The complete lack of toxicity of penicillin makes it an ideal drug for use in aged individuals.

Of nine cases reported here, and included in the active group with bacteriemia, six were treated intensively by the older methods. Case 3 was given sulfapyridine without benefit. Case 4, in which the causative organism was *H. parainfluenzae*, was under observation with intermittent administration of sulfadiazine for over one year. He seemed at times to be definitely benefited by the sulfonamide therapy, and it probably prolonged his life. In Case 5 sulfapyridine, sulfathiazole, and hyperthermia were without effect. In Case 7 sulfapyridine and sulfathiazole produced a brief temporary sterilization of the blood stream. In Case 8, the patient received sulfadiazine and seven hyperthermia treatments without any improvement. In Case 9 the patient was given sulfadiazine intravenously without effect on the clinical course.

SUMMARY

The literature relating to the incidence of bacterial endocarditis among the aged has been reviewed. Eighteen cases of this disease in persons ranging in

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The writer gratefully acknowledges the friendly cooperation of the Department of Pathology, Montefiore Hospital, New York City, in furnishing the post-mortem findings in Cases 3 and 8.

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heart disease other than sickle-cell anemia. Patients who were receiving digitalis, quinidine, morphine, insulin, xanthine derivatives, diuretics, or salicylates were not included.

All patients had a thorough cardiac survey, including electrocardiographic, fluoroscopic, and teleroentgenographic examination, as well as a complete hematologic investigation. The diagnostic parameters, $\triangle_1$ and $\triangle_2$, were ascertained routinely in most of the cases.[7]

The electrocardiograms were recorded by means of the Hindle galvanometer.* The standard and precordial leads were analyzed in the usual way for the amplitude and duration of the respective complexes. All electrocardiograms were taken with the patient in the supine position, and all records were properly standardized.

Of eighty-five patients with sickle-cell anemia, twenty-five were suitable for study. The cardiac state of these patients was studied from the clinical and electrocardiographic points of view. The average age was 13 years. The youngest was 1, and the oldest, 27 years. Forty per cent of the patients were females. In addition, the pathologic changes were studied in nine other post-mortem subjects.

The normal values for the electrocardiograms used for comparison in these studies are taken from the work of Ashman and his collaborators.[8, 9] All normal values given are for adults unless stated otherwise.

RESULTS

I. *Clinical.*—The clinical cardiac data are shown in Tables I, II, and III. The blood pressures averaged 112/71, and varied between 94/50 and 130/80.

TABLE I. CLINICAL AND ELECTROCARDIOGRAPHIC OBSERVATIONS ON TWENTY-FIVE PATIENTS WITH SICKLE CELL ANEMIA

PATIENT	AGE (YR.)	SEX	RBC (MILLION)	PULMONARY CONUS	RV	LV	CT RATIO (%)	CARDIAC RATE (BEATS/MIN.)	ANATOMIC AXIS (DEGREES)	AXIS DEVIATION OF THE QRS (AREAS, DEGREES)
1	18	M	2.8	0	+++	+++	59.1	80	25	37
2	6	M	3.2					114		40
3	2	M	3.0	+++	+++	++++	62.0	101	22	47
*4	22	M	2.8	++	++	+++		84		64
5	10	M	2.7	+	++	++	55.0	90	25	6
†6	12	F	2.9					60		60
‡7	10	M	3.5	0	+++	0	50.0	75	25	59
8	10	M	2.3	0	++++	++++		101	21	34
9	15	M	2.8	+++	0	+++	53.3	125	30	70
10	21	F		+++	+++	+++		76		30
11	7	M	1.4	+++	+++	++++		90		44
12	21	F	2.3	++	++++	++	56.6	83	45	61
13	10	F	1.8	+	++	+++	45.5	86	21	47
14	25	F	1.5				65.0	70		50
15	10	F		+	+++	++	60.0	110		72
§16	6	F	1.8	+++	+++	+++	60.8	86		125
17	6	F		++	+++	++	57.0	94	22	40
18	4	M	2.3	+	++	++		90		54
19	27	M	1.7	0	0	0		57		47
20	1	M	3.5	++	+++	+++		125	12	58
21	15	M	1.0	+	+++	+++		88		0
‖22	14	M	2.7	0	0	++		101		53
23	26	F	2.0	0	++	++		80	18	10
24	16	M	1.9	++++	++++	++++	65.0	80	30	50
25	13	F	2.0	++	++	++++	54.0	104	30	51
Mean	13.0		2.4				57.2	90	27.3	19.5
Maximum	27.0		3.5				65.0	125	45.0	125.0
Minimum	1.0		1.0				45.5	60	18.0	0.0

Abbreviations: RV = right ventricle.
LV = left ventricle.
CT = cardiothoracic.

*Q-T interval greater than normal by 0.05 second.
†P-R interval greater than normal by 0.01 second.
‡P-R interval greater than normal by 0.02 second.
§Deviation of QRS axis +125 degrees. Clinically, pulmonary infarction.
‖P-R greater than normal by 0.02 second. T_1 low.

*Cambridge Instrument Company, Ossining, New York.

THE ELECTROCARDIOGRAM AND CARDIAC STATE IN ACTIVE SICKLE-CELL ANEMIA

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THIRTY years have passed since Herrick described the first cases of drepanocytic anemia.[1] During this time much has been written about this interesting disease. Approximately 145 articles, containing 388 reports of active cases with anemia, have appeared.[2] Only four of these articles, however, deal with the cardiac aspect of this condition.[3-6] There has been no detailed analysis of the electrocardiographic changes in this disease, although many of the case reports have included isolated electrocardiograms. Since an adequate number of patients with active sickle-cell anemia who have been repeatedly examined carefully cardiologically during a period of three years were available for further investigation, it was considered advisable to study the cardiac state and the electrocardiogram in this disease.

At first glance it would appear that this type of cardiac disease affects only a few members of the Negro race. This is not true in the South. During a single year, 1941 to 1942, at Charity Hospital in New Orleans, forty patients with this disease were admitted to the wards. The great majority of these patients had heart disease. It is to be noted that, among the Negro patients at Charity Hospital, heart disease in sickle-cell anemia is encountered more frequently than heart disease due to beriberi, myxedema, periarteritis nodosa, trauma, or pernicious anemia. The apparent infrequency with which heart disease in sickle-cell anemia is encountered seems to be due to the fact that this condition is often unrecognized. It is frequently confused with rheumatic heart disease, congenital heart disease, or bacterial endocarditis.

The problem of heart disease in sickle-cell anemia is not confined entirely to persons with Negroid characteristics, for it has been observed in patients who are "socially" white, and in such cases the diagnosis is rendered more difficult. Whether or not sickle-cell anemia occurs among persons who are free from Negro blood is difficult to ascertain. Nevertheless, neither color nor racial features rule out the possibility of sickle-cell anemia heart disease.

Heart disease in sickle-cell anemia is one of the few types of heart disease which is hereditary. Once the diagnosis of sickle-cell anemia is established in a family, heart disease should be considered in all other members of the group.

It is because of the paucity of information dealing with heart disease in sickle-cell anemia, the frequency of this condition in localities where there is a substantial Negro population, and the frequency with which this type of heart disease is overlooked that the cardiac state and the electrocardiographic picture are discussed.

METHODS AND MATERIALS

This study includes only patients with active sickle-cell anemia. Patients with any of the following complications were excluded: acquired or congenital syphilis, a blood pressure or more than 140 mm. Hg, systolic, or 90, diastolic, an erythrocyte count greater than 3,500,000, a history of diphtheria or any other severe infection, or any discernible cause for

Received for publication Aug. 28, 1944.

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TABLE IV. NECROPSY OBSERVATIONS IN NINE CASES OF SICKLE-CELL ANEMIA

PATIENT	AGE (YR.)	SEX	NECROPSY FINDINGS			REMARKS
			HEART	LUNGS	LIVER	
1	17	F	Weight, 440 grams. Marked left ventricular dilatation. Marked interstitial edema. Sickling of erythrocytes	Grossly edematous. Polymorphonuclear infiltration about bronchi	Weight, 3,080 grams. Grossly brown homogeneous appearance. Microscopically small yellow crystalline deposits within hepatic cells	Died six days postoperatively
2	10	F	Weight, 225 grams. Marked dilatation of right auricle and ventricle. Flattening of trabecular carnae. Zenker's degeneration. Polymorphonuclear interstitial infiltration	Moderate obliterative endarteritis	Weight, 795 grams. Moderate chronic passive congestion	Died four days postoperatively following removal of thyroglossal duct cyst
3	32	M	Weight, 430 grams. Marked dilatation of right and left ventricles. Flabby myocardium. Obliterative endarteritis of coronary and pericardial vessels. Vacuolization of sarcoplasm	Pulmonary edema. Obliterative endarteritis of occasional pulmonary arteriole	Weight, 1,350 grams. Extreme collapse necrosis. Sickling present	Died in coma following fainting attacks. Congestive heart failure
4	25	F	Weight, 350 grams. Dilated right and left ventricles. Grossly beefy red. Interstitial edema	Obliterative endarteritis of occasional pulmonary arteriole	Extreme chronic passive congestion	Died two days postoperatively
5	22	M	Weight, 350 grams. Dilated right and left ventricles. Interstitial edema	Pulmonary edema, slight pulmonary arteriolar thrombosis	Weight, 1,450 grams. Firm fatty change	Died following laparotomy for supposed ruptured peptic ulcer
6	23	M	Weight, 370 grams. Right and left ventricular dilatation. Heart beefy red	Pulmonary edema	Weight, 3,200 grams. Slate brown	Died five hours after blood transfusion
7	30	M	Weight, 390 grams. Right and left ventricular dilatation. Interstitial edema. Vacuolated sarcoplasm	500 c.c. of pleural effusion bilaterally. Marked pulmonary edema	Weight, 1,680 grams. Extreme chronic passive congestion	Congestive heart failure
8	35	M	Weight, 360 grams. Dilated right auricle and ventricle. Myocardial degeneration	Thrombosis of pulmonary arterioles in some areas	Nutmeg appearance	Congestive heart failure
9	18	F	Right ventricular dilatation. Myocardial degeneration	Pulmonary edema. Moderate thrombosis of pulmonary arterioles	Hepatomegaly with infarction	Died twelve hours postoperatively

hearts, and an equal number showed degenerative changes in the myocardium. Myocardial degeneration was evidenced by vacuolization of the sarcoplasm, disappearance of the muscle striation, and Zenker's degeneration of the myofibrils. Five patients of the autopsy series (55 per cent) had definite dilatation of both the right and left ventricles. Three (35 per cent) had dilatation of the right ventricle and one (11 per cent) had dilatation of the left ventricle alone.

The muscle fibers were separated by edema fluid, with or without an increase in the amount of interstitial tissue, in three (33 per cent) of the cases.

The average erythrocyte count was 2,400,000, and the extremes were 1,000,000 and 3,500,000 cells per cubic millimeter. The diagnostic parameters averaged 49 mm. per hour, and varied between 32 and 72 millimeters.

Cardiac murmurs were present in 95 per cent of the group (Table II). Dyspnea on exertion and a cardiothoracic ratio of 50 per cent or greater were present in 85 per cent of the cases. Hepatomegaly was present in 52 per cent, edema of the legs in 24 per cent, and precordial pain in 15 per cent. There was some degree of cardiac enlargement in 95 per cent of the cases as ascertained fluoroscopically. The left ventricle was enlarged in 91 per cent of the cases, the right ventricle in 86 per cent, and the pulmonary conus in 73 per cent.

TABLE II. CARDIAC SIGNS AND SYMPTOMS IN TWENTY-FIVE CASES OF SICKLE-CELL ANEMIA

SIGN OR SYMPTOM	FREQUENCY (PER CENT)
Temperature of 100° or over	95
Cardiac enlargement	
Left ventricular	91
Right ventricular	86
Pulmonary conus	73
Cardiac murmurs	95
Dyspnea on exertion	85
Cardiothoracic ratio 50 per cent or greater	85
Hepatomegaly	52
Leg edema	24
Precordial pain	15

TABLE III. TYPES OF CARDIAC MURMURS IN TWENTY-FIVE CASES OF SICKLE-CELL ANEMIA

MURMUR	FREQUENCY (PER CENT)
Mitral systolic	48
Pulmonary systolic	19
Aortic systolic	14
Aortic systolic and diastolic	5
Pulmonary systolic and diastolic	5
Mitral systolic and diastolic	5
Thrill (mitral)	5

The types of cardiac murmurs are summarized in Table III. In general, the murmurs were loud, and were a prominent physical sign. Mitral systolic murmurs occurred in 48 per cent of the cases. These murmurs were frequently transmitted over the entire precordium and posterior aspect of the thorax. In 5 per cent the mitral systolic murmur was associated with a presystolic rumble. Pulmonary systolic murmurs occurred in 19 per cent of the cases. In 5 per cent there was a systolic and a diastolic pulmonary murmur. Accentuation of the pulmonary second sound was frequently present. An aortic systolic murmur occurred in 14 per cent of the cases, and, in 5 per cent, there were an aortic systolic murmur and an early, soft, blowing, aortic diastolic murmur. A mitral thrill was present in 5 per cent of the cases.

The anatomic axis of the ventricles (obtained from teleroentgenograms), as measured through the main muscle mass of the ventricles, averaged 27.3 degrees and varied between 45 and 18 degrees (Table I).

II. *Pathologic Data.*—Nine autopsied patients (Table IV) were studied from the standpoint of cardiovascular changes. Two of the patients died after surgical procedures, three died after childbirth, three died of congestive heart failure, and one died after a blood transfusion. The average age at death was 24 years, and the extremes were 10 and 35.

The mean, maximum, and minimum cardiac weights were 361, 440, and 225 grams, respectively. Seven (78 per cent) of the patients had dilated, thin, flabby

amplitudes are 0.55, 1.25, and 0.80 mm., respectively. The upper limits of normal amplitudes are considered to be 1.1, 2.5, and 2 mm., respectively, for Leads I, II, and III.) In five (20 per cent) of the cases of active sickle-cell anemia the height of the P wave in Lead I was greater than 1 millimeter.

There was slight notching of the apex of the P wave in five (20 per cent) of the cases. In no instance did the notch return as far as halfway to the isoelectric line. (Slight notching occurs in about 32 per cent of normal subjects.)

The P wave was diphasic or inverted in Lead CF_1 in five (15 per cent) of the cases in which CF_1 leads were taken. The P wave was negative in Lead IVF in two (20 per cent) of the cases. The average amplitude of P in this lead was 0.3 millimeter. The percentages of patients with diphasic or inverted T waves in Leads CF_2, CF_3, CF_4, and CF_5 were 33, 25, 22, and 22 per cent, respectively. Thus the P wave exceeded the upper limit of normal for duration in 4 per cent of the cases, and it exceeded the upper limit of normal for amplitude in 20 per cent.

P-R Interval.—The P-R interval in the twenty-five cases averaged 0.15 second, and varied between 0.19 and 0.12 second. (The normal, mean P-R interval is 0.15 second.) The average cardiac rate was 90 beats per minute, and the extremes were 60 and 125.

Six patients (patients 4, 10, 12, 14, 19, and 23, Table I) were 21 years of age or more. The average P-R interval of these patients was 0.15 second, and the extremes were 0.14 and 0.17. The cardiac rates varied between 57 and 84 beats per minute. In no instance did the P-R interval reach the upper limit of normal. Two of the patients were under 2 years of age and had normal P-R intervals.

The remaining seventeen patients were children ranging in age from 6 to 16 years. Their cardiac rates varied between 60 and 125 beats per minute. The average P-R interval for this group was 0.15 second, and the extremes were 0.13 and 0.19 second. The interval in three of these cases (Patients 6, 7, and 22, Table I) exceeded the upper limit of normal by 0.01, 0.02, and 0.02, respectively. Patient 5 reached, but did not exceed, the upper limit of normal of 0.17 second.

In the chest leads the interval was not significantly different from the standard leads. The average interval for all of the precordial leads was 0.15 second. The range extended from 0.12 to 0.19 second. Thus, of the entire twenty-five patients, three (12 per cent) had P-R intervals which exceeded the upper limit of normal.

QRS Complex.—In only one instance did the duration of the QRS interval reach, but did not exceed, the upper limit of normal (Patient 3). The duration of the QRS interval of the two infants was 0.06 and 0.05 second, respectively. In the adults, the average duration was 0.07 second, and varied between 0.06 and 0.08 second. In the remainder, the child-adolescent group, the average duration was 0.06 second, and it varied between 0.05 and 0.08 second. (The upper limit of normal is 0.10 second.)

In the chest leads the duration of the QRS complex was slightly longer than in the standard leads. The average duration for the six chest leads was 0.08 second. The extremes were 0.05 and 0.10 second. Thus, in no instance was the QRS interval abnormally long.

Q Wave.—The amplitude of the Q wave in Lead I averaged 0.62 mm., and varied between 0 and 3. In Lead III the amplitude averaged 1.08 mm., and varied between 0 and 5. The maximum amplitudes in Leads I and III did not occur in cases of extreme right or left axis deviation. In Patients 2 and 12, Q_3 was more than one quarter the amplitude of the highest R wave of the standard leads. The duration of Q did not reach 0.02 second in any instance. In one instance the Q wave was present in all leads.

The Q wave was absent in all CF_1 leads. There was a progressive increase in the amplitude of the Q wave as the exploring electrode passed from the right to the left side of the precordium. The average Q wave in Lead IVF was 2.9 millimeters. The deepest Q wave in this lead measured 16 millimeters. In no case was the Q wave indicative of heart disease.

R Wave.—The highest R wave in the three standard leads measured 22 mm., and the lowest, 1 millimeter. The normal range is 1 to 23 millimeters. Notching of the R wave was present in 50 per cent of the cases in Lead III. In no instance did the duration of the R wave exceed 0.04 second.

The amplitude of the R wave averaged 4.6 mm. in CF_1. The amplitude of the R wave increased as the exploring electrode was moved from the right to the left side of the chest. In Lead IVF the average amplitude was 24.4 millimeters. The amplitude of the R waves in the chest leads did not exceed the upper limit of normal in any case. Thus the amplitude and duration of the R wave were not in any instance abnormal.

In one instance (Patient 3, Table IV) there was obliterative endarteritis of one of the small branches of the coronary artery. In the same case, a pericardial vessel showed occlusion from thrombosis and endarteritis.

The pulmonary arterial vessels showed endarteritis in varying degrees in six (66 per cent) of the cases. The degree of pulmonary endarteritis and thrombosis was for the most part slight, but was occasionally moderate in degree. In no instance was it marked. Sickling of the erythrocytes was frequently demonstrated within the pulmonary vessels. Six (66 per cent) of the necropsy series showed marked pulmonary edema, both grossly and microscopically. Only one patient (11 per cent) had pleural effusion. This patient (Patient 7, Table IV) had 500 c.c. of straw-colored fluid in each pleural cavity.

The mean, maximum, and minimum weights of the livers were 1,926, 3,200, and 795 grams, respectively. The livers showed chronic passive congestion in six (66 per cent) of the cases. In two cases (Patients 3 and 7, Table IV) hepatic cell necrosis was so severe that only about 25 per cent of the hepatic cells were definitely distinguishable.

III. *The Electrocardiogram.*—The results of the routine analysis of the electrocardiograms of twenty-five patients are shown in Table V. Precordial leads were recorded in the majority, but not in all, of the twenty-five cases.

TABLE V. ELECTROCARDIOGRAPHIC DATA IN TWENTY-FIVE CASES OF SICKLE-CELL ANEMIA

(Each compartment contains mean, maximum, and minimum values for each component of the electrocardiogram.)

LEAD	P		P-R	QRS				S-T	T	Q-T
	DURATION (SEC.)	AMPLITUDE (MM.)	INTERVAL (SEC.)	DURATION (SEC.)	AMPLITUDE Q (MM.)	AMPLITUDE R (MM.)	AMPLITUDE S (MM.)	SEGMENT (SEC.)	AMPLITUDE (MM.)	INTERVAL (SEC.)
I	0.084	0.950	0.153	0.065	0.624	10.680	1.220	0.094	1.684	0.339
	0.120	1.800	0.190	0.080	3.000	15.000	9.000	0.160	4.000	0.420
	0.040	0.120	0.120	0.050	0.000	4.000	0.000	0.030	0.200	0.280
II	0.096	1.204	0.152	0.065	0.120	14.320	0.960	0.092	2.576	0.316
	0.120	2.200	0.190	0.100	2.000	22.000	5.000	0.160	6.200	0.420
	0.000	0.000	0.130	0.040	0.000	4.000	0.000	0.000	0.500	0.280
III	0.056	0.264	0.153	0.066	1.080	6.780	1.256	0.108	1.036	0.323
	0.110	1.700	0.190	0.080	5.000	15.000	10.000	0.180	3.000	0.420
	0.000	-0.600	0.120	0.050	0.000	1.000	0.000	0.000	-0.400	0.280
CF_1	0.065	0.500	0.156	0.081	0.000	4.610	16.450	0.059	-3.410	0.350
	0.100	1.500	0.190	0.100	0.000	10.000	30.000	0.120	-6.000	0.400
	0.040	-2.00	0.120	0.070	0.000	2.000	7.500	0.040	-1.100	0.320
CF_2	0.073	0.440	0.154	0.081	0.111	9.331	24.390	0.084	-3.633	0.349
	0.110	1.000	0.190	0.100	1.000	14.000	33.000	0.120	1.000	0.400
	0.040	-0.300	0.120	0.070	0.000	4.000	18.500	0.020	-8.000	0.320
CF_3	0.054	0.225	0.144	0.081	0.125	15.000	11.500	0.072	-1.501	0.352
	0.060	0.500	0.190	0.100	1.000	18.000	26.000	0.120	5.000	0.400
	0.000	-0.200	0.130	0.070	0.000	5.000	2.000	0.000	-2.500	0.320
CF_4	0.050	0.200	0.154	0.011	1.380	15.125	6.777	0.066	1.222	0.349
	0.100	0.500	0.190	0.100	3.000	22.000	15.000	0.120	8.000	0.400
	0.040	-0.200	0.120	0.060	0.000	5.000	1.000	0.000	-3.000	0.320
CF_5	0.045	0.240	0.154	0.081	2.350	19.200	2.200	-0.044	2.330	0.350
	0.100	1.000	0.190	0.100	5.000	34.000	10.000	0.160	6.000	0.400
	0.000	-0.200	0.120	0.070	1.000	6.000	0.000	0.000	0.000	0.320
IVF	0.037	0.300	0.156	0.070	2.910	24.430	9.700	0.056	1.555	0.322
	0.080	1.000	0.190	0.100	16.000	30.000	24.000	0.140	14.000	0.400
	0.000	-0.200	0.130	0.050	0.000	7.000	0.000	0.000	-10.000	0.280

P Wave.—The mean value for the duration of the P wave was 0.096 second in Lead II; the maximum was 0.12 second. (The normal average for adults is 0.08 second, and varies between 0.06 and 0.11 second. The upper limit of normal is considered to be 0.10 second.) Only one patient (Patient 6, Table I) exceeded the upper limit of normal.

The greatest amplitude of the P waves was present in Lead II. The average amplitudes for Leads I, II, and III were 0.95, 1.20, and 0.26 mm., respectively. (The average normal

T Wave.—The T waves were upright in all instances in Leads I and II, and in 78 per cent of the cases in Lead III. The average amplitude in Lead I was 1.7 mm., and the maximum was 4 millimeters. (The average amplitude in Leads I and II in normal subjects is 2 and 3 mm., respectively.) In Lead I the lowest T waves were encountered in Patients 12 and 22, who had amplitudes of 0.5 and 0.2 mm., respectively. The average amplitude for the twenty-five patients in Lead II was 2.6, and the maximum amplitude was 6.2, millimeters. (The normal mean is 3 millimeters.) Patients 22 and 23 had T waves in Lead II which were 0.5 and 0.8 mm., respectively. In the remaining cases the T waves in Lead II were over 1 mm. in amplitude. The average amplitude in Lead III was 1, and the maximum, 3, millimeters. (The mean for normals is 1.2 millimeters.) One patient, Patient 25, had a negative T wave in Lead III of -0.4 millimeter. Two patients, 1 and 20, had diphasic T waves in this lead. None of the T waves were sharply inverted in the standard leads.

In Patients 12, 21, and 22, T_3 was slightly higher than T_1. The electrical axes of the QRS in these cases were 61, 0, and 53 degrees, respectively. Patient 21 had a T_1 which measured 1 mm., and T_3 measured 2.1. All patients except this one had a QRS axis greater than 30 degrees. In Case 22 the highest T wave of the three leads was 0.5 millimeter. All other patients had T waves of 1.3 mm. or more. Ashman found that only seven of one hundred normal subjects had T waves with the greatest amplitude in all three leads of 1.5 mm. or less. Notched T waves were noted in Case 25. Rounding of the T waves was present in Case 21.

In the chest leads, the average amplitude of the T waves in Leads CF_1, CF_2, and CF_3 was -3.4, -3.6, and -1.5 mm., respectively. In Leads CF_4, CF_5, and IVF the averages were 1.2, 2.3, and 1.6 mm., respectively. In Leads CF_4 and IVF the T waves were inverted or diphasic in four cases (40 per cent), whereas, in CF_5, the T wave was diphasic in two instances (20 per cent). In only one instance was the amplitude of T greater than the normal value of 13 mm. for men, or 9 mm. for women. Thus, the T waves were abnormally low in one case in the standard leads, and the T wave was slightly increased in amplitude in Lead IVF. In Leads CF_4 and IVF the T waves were inverted or diphasic in four, or 40 per cent, of the subjects.

Q-T Interval.—When sinus arrhythmia was marked, the averages of more than one interval were recorded. The Q-T interval exceeded the normal in one instance by 0.05 second.

ELECTROCARDIOGRAPHIC CHANGES IN FOUR CASES WITH SERIAL ELECTROCARDIOGRAMS

The electrocardiogram was recorded serially in four cases over periods of observation varying from three to four years. Only one showed any significant changes, which are as follows:

In Case 16, serial electrocardiograms (Fig. 1) showed cardiac rates that varied between 88 and 125 beats per minute. The P waves and the P-R and Q-T intervals were within normal limits. There was definite right axis deviation (areas). The T waves in Leads IVF were upright in the first two electrocardiograms. The electrocardiograms taken Dec. 3, 1941, and May 3, 1943, had sharply inverted T waves in Lead IVF. There was no significant shift of the S-T segment.

DISCUSSION

It is apparent that sickle-cell anemia heart disease is essentially a disease of young people. The average age was 13 years for the living group, and 24 years for the autopsy group. The youthful age at which sickle-cell anemia cardiac disease occurs accounts for the frequent confusion with rheumatic heart disease and congenital heart disease.

Cardiac enlargement was almost universal in these cases, as ascertained fluoroscopically, roentgenographically, and at necropsy.

The type of cardiac enlargement may frequently aid in differentiating sickle-cell anemia heart disease from rheumatic mitral stenosis or other types of heart disease. In no instance in the cases of heart disease due to sickle-cell anemia was there enlargement of the left auricle. The electrocardiogram showed right axis deviation in only one instance. These facts aid in eliminating mitral

S Wave.—The deepest S wave in the three standard leads was studied. The average was 1.26 mm., and the extremes were 0 and 10.

In the chest leads the S waves were large in electrocardiograms taken on the right, and small in those taken on the left side of the chest. The average amplitude of the S wave in Leads CF_1, CF_2, CF_3, CF_4, CF_5, and IVF was 16.5, 24.4, 11.5, 6.8, 2.2, and 9.7 mm., respectively.

In Lead CF_1 the upper limit of normal of 20 mm. in amplitude was exceeded by three patients (30 per cent). In CF_2 it was exceeded in six cases (60 per cent), and in CF_3 it was exceeded in two cases (20 per cent). The maximum amplitude was 33 mm in CF_2.

The Electrical Axis of the QRS Complex.—The electrical axis of the QRS complex averaged 49.5 degrees, and varied from 0 to +125 degrees. Patient 16, Table I, had a deviation of +125 degrees. This patient was a 6-year-old girl who, at the time the electrocardiogram was taken, had an attack of pulmonary pain which was interpreted as the result of pulmonary infarction. Serial electrocardiograms are shown in Fig. 1. The electrical axis was abnormal in only one (4 per cent) of the series. The deviation in this case was to the right.

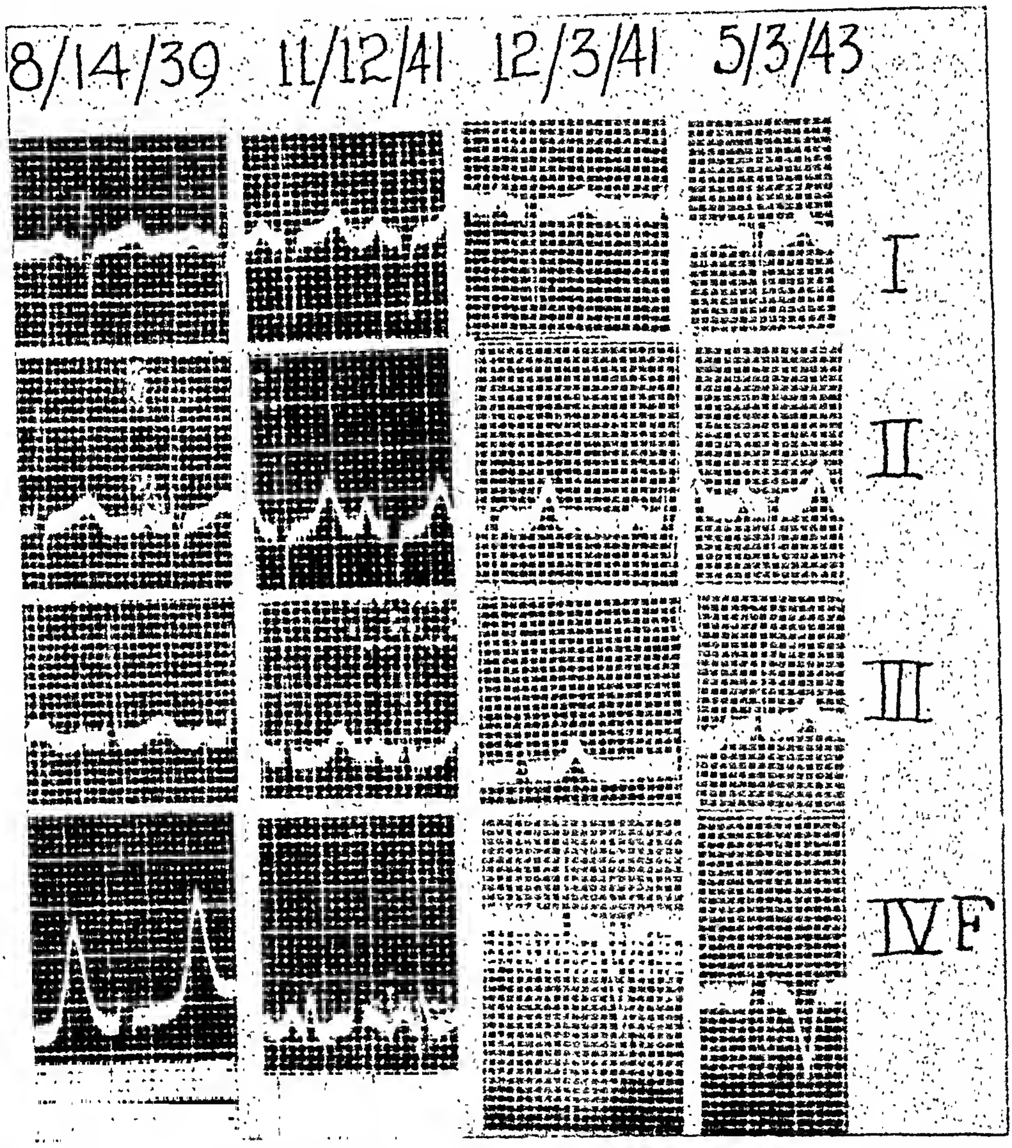

Fig. 1.—Serial electrocardiograms of Patient 16. There is right axis deviation (determined by measuring areas) of the QRS. This is the only instance of abnormal right axis deviation in this series. This figure shows a marked change in the T wave in IVF during the four years of follow-up.

S-T Segment.—The amplitude averaged 0.092 second in Lead II, and varied between 0 and 0.16 second. The average duration for males was 0.088 second, and the average cardiac rate was 87.1 beats per minute. The length of the segment for females averaged 0.096 second, and the average cardiac rate was 85.1 beats per minute. Those with the fastest rates had the shortest S-T segments.

The S-T segment in the chest leads did not vary significantly from the values indicated for the standard leads. In no instance was the segment greater than the upper limits of normal for the cardiac rate and sex. In no instance did the segment deviate 1 mm. or more from the isoelectric line in any lead.

2. Disturbances of cardiac function.

3. Disappearance of signs and symptoms after relief of the anemia.

In many anemias these criteria are met. In sickle-cell anemia one deals with an anemia which is, using present-day methods, somewhat refractory to treatment. Criterion *3* cannot be satisfactorily met except for short periods of time. In this disease severe grades of anemia remain, and result in severe strain upon the heart for years. One cannot expect these changes to be reversible unless the anemia is reversible. It is obvious that, in sickle-cell anemia, the same factors are at work as in other anemias, and, in addition, the changes are accentuated by the refractory nature of the anemia, coupled with the fact that it is compatible with many years of life. The cause and effect relationship of the anemia and cardiac abnormalities cannot be denied.

In addition to what is noted above, certain cardiac changes occur which differ somewhat from the usual cardiac expressions of ordinary clinical forms of anemia. These include the rather constant enlargement of the right ventricle and pulmonary conus. Yater and Hausman[4] and Klinefelter[6] have stated that this may be associated with pulmonary vascular lesions. It has, however, been demonstrated that similar changes occur in severe and prolonged anemias of other types.[10] Goldstein and Boas,[11] in 1927, reported that twenty-three of thirty-nine patients with pernicious anemia had cardiac enlargement. In twelve who came to autopsy there was dilatation of all chambers, and, in four, definite enlargement of the pulmonary conus. Their incidence of patients with cardiac enlargement was 57 per cent of the series, and is slightly less than that encountered in our series. They offered no explanation for the relative frequency of right ventricular dilatation in their cases. Such observations indicate that heart disease and right ventricular enlargement appear in other types of anemia, and are not yet explained entirely as a result of pulmonary changes. In fact, the pulmonary changes encountered in this series did not seem to be of sufficient degree consistently to produce the picture of cor pulmonale. In this series the left and right ventricles were enlarged, and evidence of left ventricular failure was as frequent as was evidence of right ventricular failure. The normal axis deviation of the QRS complexes, except in isolated cases, as well as the normal anatomic axis, perhaps indicates that the anemia per se is the important and usual cause of the clinical and pathologic evidence of cardiac disease in this disease, and not pulmonary or coronary arteritis. In unusual instances pulmonary arteritis may produce pulmonary heart disease, as was probably the case in Patient 16, Table I.

In many of the patients of this series no cardiac diagnosis was made until very late in the course of study. Hamman[3] emphasized the importance of being extremely cautious in making a nonanemia diagnosis of heart disease when studying a patient with sickle-cell anemia. One should be equally cautious in the interpretation of any sort of murmurs in the presence of severe, active, sickle-cell anemia, and wait until the anemia is under control.

Routine analysis of the electrocardiogram revealed only nonspecific, and rather inconsistent, changes. The electrocardiograms were slightly suggestive in 4 per cent of the cases, and definitely abnormal in another 16 per cent. Serial electrocardiograms sometimes showed additional evidence of myocardial change, although this was not the rule. There was no characteristic electrocardiographic pattern of the heart disease of patients with sickle-cell anemia. In general, the changes were those frequently encountered in cases of severe anemias or any toxic myocardial state. Cardiac arrhythmias of any type were distinctly

stenosis. The pulmonary conus was frequently prominent, and was particularly noticeable when there was evidence of pulmonary infarction. This produced a roentgenographic picture similar to that in cases of cor pulmonale produced by other types of pulmonary disease.

Cardiac murmurs occurred with great regularity. Mitral, pulmonary, and aortic murmurs, either systolic, or diastolic, or both, were encountered. A definite thrill was palpated in one case. This patient had mitral systolic and diastolic murmurs, and had no evidence of rheumatic fever; the cardiac signs were explainable entirely as a result of sickle-cell anemia.

Dyspnea on exertion was a common manifestation. Cardiac enlargement, a rapid pulse rate, fine, moist râles in the lungs, hepatomegaly, and edema of the ankles suggested right and left ventricular failure. All of these abnormalities, however, were often explainable as a result of severe anemia, pulmonary infarction, and hepatic changes due to sickle-cell disease. Severe right or left ventricular congestive heart failure, with severe orthopnea, was not encountered in any of the cases of this series. The presence of the sickle-cell anemia always made it difficult to evaluate the degree of cardiac decompensation because the disease itself may simulate this condition (vide supra).

Severe precordial pain, like orthopnea, was a relatively infrequent complaint. When it occurred it was difficult to ascertain its mechanism, that is, whether it was due to coronary arteritis from sickle-cell anemia, anemia per se, or other states, such as pulmonary crises due to sickle-cell anemia.

The pathologic changes in the myocardium consisted of marked interstitial edema, degeneration of the sarcoplasm, and thinning and dilatation of the right auricle and ventricle. In one case, there was endarteritis of the coronary arterioles and arteries of the pericardium. Over half (66 per cent) of the autopsied patients had endarteritis of the pulmonary vessels, although this was slight in many cases. Pulmonary edema was common. Hepatomegaly was not uncommon, and was probably caused by chronic passive congestion and specific changes due to sickle-cell anemia.

Anemia alone is probably an important factor in the production of the signs and symptoms and pathologic changes encountered in this disease. In all severe anemias the reduction in hemoglobin is accompanied by certain compensatory mechanisms, such as a greater oxygen difference in arterial and venous blood, increased cardiac output, increased pulse rate, and a more rapid circulation time. All of these tend to keep up the oxygen supply to the tissues. Because of the increased work of the heart, which is supplied by an insufficient amount of oxygen, we may expect enlargement of the heart in severe anemias. This enlargement, including both dilatation and hypertrophy, is commonly associated with fatty degeneration. Such changes have been reported many times in a variety of severe anemias, including chlorosis,[11] aplastic anemias, and pernicious anemia, especially before the advent of liver therapy. There are, however, certain changes which are not due to the anemia per se, but are peculiar to sickle-cell anemia. For example, changes in the heart may be manifestations of arteritis and endarteritis with thrombosis. Such vessel changes and the resultant parenchymal changes in the organs nourished by these vessels affect the central and peripheral circulation. These and other pathologic manifestations make sickle-cell anemia unique among the anemias.

Anemia, although neglected as a definite cause of heart disease, is a well-known one. The criteria laid down by the Criteria Committee of the New York Heart Association for the diagnosis of heart disease due to anemia are:

1. The presence of marked anemia.

An outstanding feature of the cardiac disease was cardiac enlargement, which occurred in 95 per cent of the cases. The enlargement involved for the most part the left ventricle, the right ventricle, and the pulmonary conus. In no instance was undue enlargement of the left auricle observed.

Systolic and diastolic murmurs occurred at the aortic, pulmonic, and mitral areas. A thrill occurred in one case.

Dyspnea on exertion was a frequent complaint, but orthopnea was uncommon. The pathologic specimens showed arteritis of the pulmonary, pericardial, and coronary arteries in one case, and mild pulmonary thrombosis in six of the nine subjects autopsied.

Routine analysis of the electrocardiogram showed nothing characteristic of sickle-cell anemia heart disease. Significant changes in the electrocardiogram were seen in 20 per cent of the cases when single electrocardiograms were studied in the routine manner. Serial electrocardiograms showed very few changes over periods of approximately four years.

Definite right axis deviation occurred in only one case, although enlargement of the pulmonary conus or right ventricle was encountered in 73 and 88 per cent of the cases, respectively.

Premature beats were encountered in only two cases. No other cardiac arrhythmias, other than sinus arrhythmia, were seen.

The P waves showed about the same degree of notching as is encountered among normal subjects.

The P-R interval surpassed the upper limit of normal in 12 per cent of the cases. Complete A-V block and bundle branch block were not present in this series.

Only 4 per cent of the patients had a low T wave in Lead I.

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unusual. Premature beats were the only disturbances in cardiac mechanism encountered in the entire series.

Right axis deviation occurred in one case at a time when a clinical diagnosis of pulmonary infarction was made. Right axis deviation in this series was rarely an accompaniment of sickle-cell anemia heart disease; it occurred only once in twenty-five instances, in spite of the fact that enlargement of the right ventricle and pulmonary conus occurred in 86 per cent and 73 per cent of the cases, respectively. Also, in 88 per cent of the necropsy cases there was dilatation of the right ventricle, and none of these patients had had abnormal deviation of the QRS axis. Six of the necropsy patients showed mild or moderate pulmonary arteritis and thrombosis. None of these patients had abnormal axis deviation.

The P waves showed little deviation from the normal. They were occasionally of slightly increased amplitude and duration. The degree of notching was not greater than that found in normal subjects. In cases of rheumatic fever there is a somewhat greater tendency to widening and notching of the P waves.

The P-R interval surpassed the upper limits of normal in 12 per cent of the cases. However, in no instance was the P-R interval markedly prolonged, as sometimes occurs in other clinical states. In no instance was complete A-V block or bundle branch block seen. The duration of the QRS complex was within normal limits in all instances, and the Q-T interval was long in only one instance.

T waves suggestive of abnormalities were encountered in 20 per cent of the cases. These changes were generally borderline, and were not as a rule markedly abnormal. They varied from low T waves in Lead I to a low T_2, a T_3 which exceeded T_1 in amplitude in the presence of left axis deviation, a T wave of 0.5 mm. height in the tallest of any of the three standard leads, rounding of the T waves, or notching of the T waves. These changes were not secondary to alterations in the QRS complex, and, therefore, were probably the result of altered repolarization due to anemia, coronary arteritis, pulmonary thrombosis, or some state peculiar to sickle-cell anemia.

In the precordial leads, inversion of T was rather commonly encountered. Since most of these patients were in the younger groups, it was difficult to ascertain the significance of this. It may have been due to the position of the heart in relation to the precordial electrode. When the T waves had been upright in previous electrocardiograms and then became negative, the changes were of greater significance.

The high incidence of cardiac deaths at autopsy for the most part can be readily accounted for by the fact that severe myocardial disease was present in these cases. Anoxemia, shock, pulmonary or coronary thrombosis, surgical procedures, anesthesia, acute blood loss, sudden increase in blood volume, infection, and the like may precipitate congestive or anginal failure in these cases.

SUMMARY

The problem of sickle-cell anemia heart disease was studied in twenty-five carefully chosen cases of active sickle-cell anemia. The pathologic changes were studied in nine others. The problem of heart disease in patients with sickle-cell anemia was discussed from the clinical, pathologic, and electrocardiographic points of view.

The electrocardiograms were analyzed in the routine manner.

The disease occurred in young adults, and it was frequently confounded with rheumatic or congenital heart disease.

was estimated for each of the points. (As in the previous papers, the areas were recorded as units, and each was 4 microvolt-seconds. One unit is the area of a small rectangle on the film when the time lines indicate 0.04 second, and when a glavanometer deflection of 1 cm. indicates a potential difference of 1 mV.)

RESULTS

A typical diagram showing the distribution of the net potential of the QRS and QRS-T complexes is shown in Fig. 1. At each tested point the upper numeral is the net QRS area in 4 microvolt-second units, and the lower numeral is the net QRS-T area. A plus sign indicates that the net area was positive, and vice versa. As nearly as could be judged from the potential distribution, an isopotential line was drawn to mark zero potential difference between the points in the line and the common terminal. The negative area in the QRS diagram, that is, the region where all the upper numbers are marked by minus signs, marks the part of the body surface upon which the net QRS area is negative;

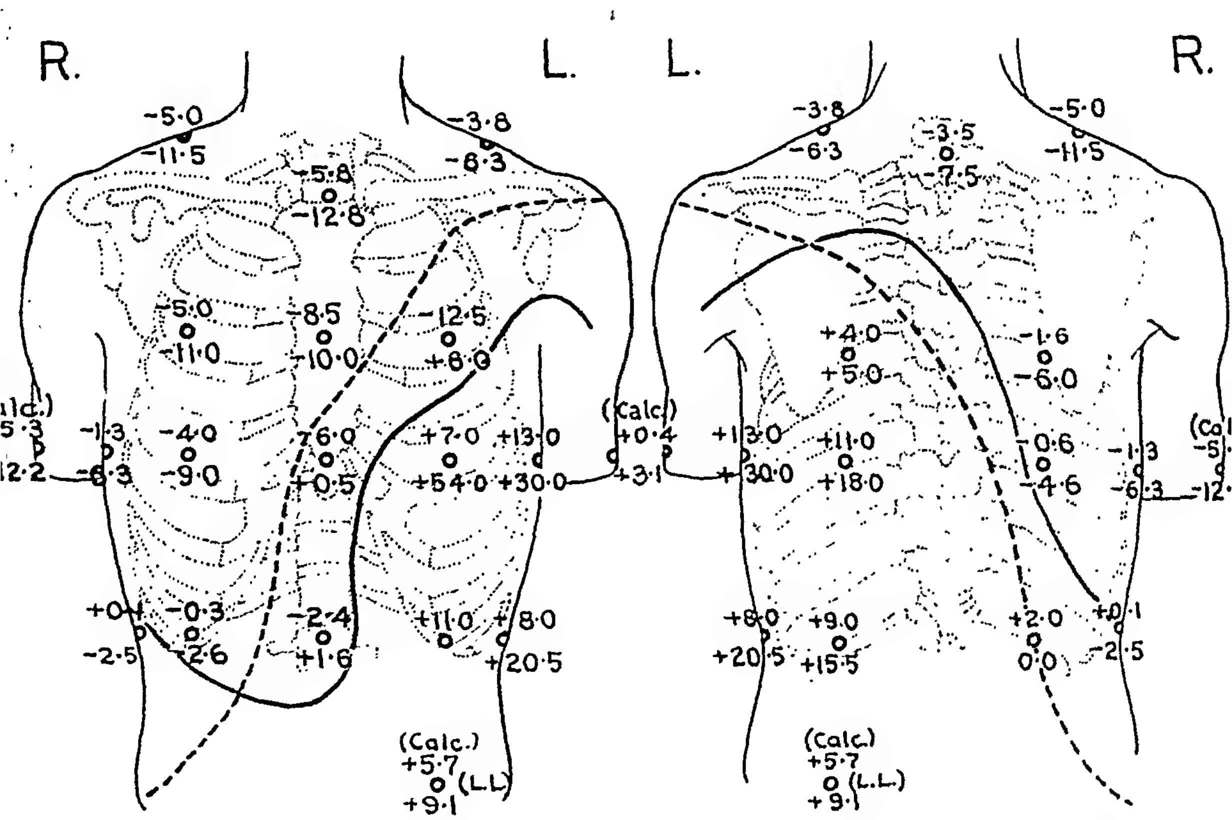

Fig. 1.—Subject 8. At each point marked by a small circle, the upper numeral is the net area, in 4 microvolt-second units, of the QRS complex; the lower numeral is the net area of QRS-T. A plus sign means that the net area was positive, relative to the common terminal, and a minus sign means that the net area was electrically negative. The solid line is the approximate line of zero potential difference between the chest potential and the common terminal for QRS, and the dotted line, similarly, is the approximate isopotential line for QRS-T.

and the positive area marks the region in which the same net area is positive relative to the common terminal. Similarly, the surface regions in which the net QRS-T area is negative and positive are shown by the lower numbers of each pair. A solid line separates the positive and negative QRS areas, and a dotted line separates the QRS-T areas. As previously reported for normal persons (lacking mirror-image dextrocardia), the right shoulder and arm are nearly always in the negative field of both the mean QRS and QRS-T axes, whereas either the left arm or the left leg may lie in either field.[7] One of our subjects (Fig. 4) was an exception.

THE NORMAL HUMAN VENTRICULAR GRADIENT

V. The Relationship Between $\hat{A}_{QRS}$ and $\hat{G}$, and the Potential Variations of the Body Surface

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In earlier papers of this series the spatial relationships between the longitudinal anatomic axis of the heart, the mean spatial QRS axis, and the spatial ventricular gradient were described.[1,2] It was inferred from the effects of rotation of the ventricles about the three possible axes of rotation that, in persons of usual body build, the mean spatial QRS axis, $S\hat{A}_{QRS}$, commonly projects posteriorly as well as downward and toward the left, and that the spatial ventricular gradient of Wilson, $S\hat{G}$, although usually also directed downward and to the left, has a less backward direction. It was calculated that, on the average, the spatial angle between $S\hat{A}_{QRS}$ and $S\hat{G}$ is nearly 30 degrees; that between $S\hat{G}$ and $S\hat{H}$, the latter being the longitudinal anatomic axis of the ventricles, the spatial angle is about 60 degrees; and that 90 degrees separate $S\hat{A}_{QRS}$ and $S\hat{H}$. The three axes were found to lie very nearly in the same plane in the normal heart of the supine, or semirecumbent, person, without tachycardia. Spontaneous tachycardia, the erect posture, or both, sometimes caused deviation of $S\hat{G}$, usually moderate in extent. More recently, ouabain has been found sometimes to cause a similar deviation.[3]

In the earlier studies these, and other, conclusions were reached from a study of limb lead electrocardiograms. No special study was made of the distribution of the net QRS or QRS-T potentials over the body surface. If the conclusions reached in the previous papers were correct, the electrical evidence for the presence of a spatial angle between $S\hat{A}_{QRS}$ and $S\hat{G}$ should be obtainable by mapping the potential changes of the body surface. Furthermore, our earlier inferences regarding the cause of individual differences in the magnitude of the manifest mean QRS axis, A_{QRS}, should receive additional support if those inferences were correct.[3,4] Incidentally, our results throw further light upon the question of the applicability of the principle of the Einthoven triangle in human electrocardiography.

METHODS

In the present study the potential changes at twenty-three points on the body surface were recorded on two patients with enlarged left ventricles, and on eight normal persons. The latter were chosen to obtain a sampling of subjects whose limb lead electrocardiograms were of contrasting types, and the positions of whose hearts differed widely. The indifferent electrode was the common terminal of Wilson, employed without the use of resistances, according to the method described by Goldberger.[5] The experimental subjects were in a semirecumbent position in a wheel chair when the curves were taken, with the exception of the two patients and one normal subject. The body surface points chosen for recording the potential changes are shown in Fig. 1, and need not be named. Since the method does not yield reliable results when the exploring electrode is much nearer to one than to the other electrodes of the common terminal, the potentials of the two arms and left leg were calculated from the three standard limb leads.[6] The net area of the QRS complex and also of QRS-T

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Received for publication Sept. 15, 1944.

face is below the point at which the perpendicular to the mean QRS-T reaches the surface, whereas the reverse holds for the back of the thorax. This, of course, is the meaning of the field differences shown in Fig. 1. Since the vectors are directed to the left, as well as backward and downward, the zero isopotential lines on the thorax usually have an oblique, rather than a horizontal, direction. In every case the degree of this obliquity agreed reasonably well with the directions of the axes, as projected upon the frontal plane and as shown by the limb leads. The results in two other cases of contrasting types are given in Figs. 3 and 4. In these figures, as in Fig. 1, at each tested surface point the upper numeral is the net QRS potential, in 4 microvolt-second units, and the lower numeral is the net QRS-T potential. The isoelectric lines are drawn as before. The legend supplies other data.

A brief description of the results follows:

SUBJECT 1.—A middle-aged white man. Syphilitic aortic insufficiency and enlarged heart. $\hat{A}_{QRS}$ and G both at −20 degrees. Little overlapping of QRS and QRS-T fields, except slightly, in the usual sense, over precordium. Anteriorly, lines extend from lower rib margin on left to about the V_2 position, thence straight upward and across left shoulder near neck, then across back of neck and down to include most of right scapula, thence to right parasternal line, downward to lower costal margin, and to starting point. Back of left shoulder is at approximate center of positive fields, thus agreeing with limb leads.

SUBJECT 2.—Age and clinical condition like Subject 1. $\hat{A}_{QRS}$, +55 degrees; G, +39 degrees. Fields, showing moderate overlap, agree well with relationships indicated by limb leads.

SUBJECT 3.—A white man about 60 years old. Chest deep, somewhat resonant, but no indication of heart disease. Illustrated in Fig. 4.

SUBJECT 4.—Young, adult, Negro male. No heart disease. Slender, but chest not flat. $\hat{A}_{QRS}$, +69 degrees; G, +63 degrees; A_{QRS}, 6.7 units. G, 14 units. Isopotential lines oblique, in front and back, from left shoulder to above right lower costal margin. Fields suggest less backward projection of mean QRS vector than is suggested by its magnitude. Subject sat up for recording of posterior potentials.

SUBJECT 5.—White man, aged 40 years. No heart disease. Hypersthenic habitus, moderately obese. Illustrated in Fig. 3.

SUBJECT 6.—White man, aged 35 years. No heart disease. Sthenic habitus. $\hat{A}_{QRS}$, +82 degrees, magnitude, 6.7 units; G, +59 degrees magnitude, 13.3 units. There is excellent agreement among the several data.

SUBJECT 7.—White man, aged, 20 years. No heart disease. Tall, sthenic, slightly obese. $\hat{A}_{QRS}$, +91 degrees, magnitude, 4.1 units; G, +64 degrees, magnitude, 10.2 units. QRS line runs from left anterior axillary fold, at first transversely, thence downward to xiphoid, and then on a straight line to right anterior axillary fold. In back the line runs from right axilla upward, to left, above left scapula and down to left axilla. In keeping with the relatively small A_{QRS}, the indicated backward projection of the vector is considerable. There is a discrepancy of 11 degrees between the mean QRS direction, at about +80 degrees, suggested by the fields, and the +91 degrees given by the limb leads. The line for QRS-T is as usual, except that the band of overlap on the back is apparently less wide than in front—a usual finding.

SUBJECT 8.—White man, aged 21 years. No heart disease. Tall, sthenic. $\hat{A}_{QRS}$, +63 degrees, magnitude, 11 units; G +46 degrees, magnitude, 22.1 units. Illustrated in Fig. 1.

SUBJECT 9.—White man, aged 20 years. No heart disease. Sthenic. $\hat{A}_{QRS}$, +65 degrees, magnitude, 8 units; G +65 degrees magnitude, 17.5 units. Isopotential line for QRS-T oblique, and slightly closer to right shoulder than usual. Overlap slight on back. Otherwise, data fully consistent.

It may be observed in Fig. 1 that a part of the positive field of QRS overlaps a part of the negative field of QRS-T or vice versa. A comparison of the lines shows that, on the front of the thorax, the line for QRS is below and to the left of the line for QRS-T, whereas on the back of the thorax, the QRS line lies above and to the right. In this subject, $\hat{A}_{QRS}$ and $\hat{G}$, the spatial axes as projected upon the frontal plane, were +63 degrees and +46 degrees, respectively. If the spatial axes coincided, the body surface fields should differ but little, if at all, in distribution. The existence of a large overlap demonstrates that the spatial axes do not coincide, but that the two spatial axes are separated by a spatial angle of fair magnitude.* Since the same kind of difference in the fields was found in all the normal subjects and in one of the patients, the results confirm the earlier conclusion. When the heart is normal the spatial angle cannot be accurately estimated from the chest potentials, yet the order of magnitude evidently agrees with the previous conclusion. The exceptional person, in whom very little difference in field distribution was found, had aortic insufficiency and a hypertrophied left ventricle.

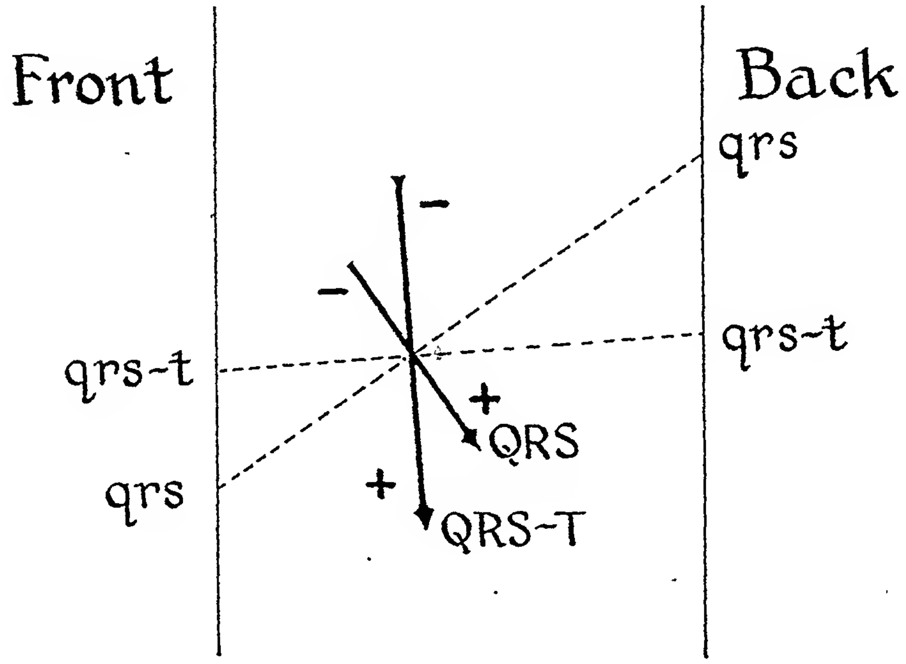

Fig. 2.—The vertical line marked "front" is the anterior chest surface, and the line marked "back" is the posterior chest surface. If the mean QRS axis has the direction shown, the isopotential lines, as shown in Fig. 1, will pass through the points marked *qrs*. These points are those at which a perpendicular to QRS reaches the surface of the thorax. The mean QRS-T axis typically points less dorsally than QRS, and the isopotential line would pass through the points marked *qrs-t*. The overlapping of the electrical fields of QRS and QRS-T, as shown in the other figures, is due to the different directions of QRS and QRS-T.

Since the spatial vectors, $S\hat{A}_{QRS}$ and $S\hat{G}$, are defined in terms of potential changes at the extremities, the vectors shown in this diagram cannot be correctly designated by those symbols.

Fig. 2 explains in diagrammatic fashion the reason for the observed difference in distribution of the electrical fields of the QRS and QRS-T complexes. When the body is viewed from the side, especially in the common case of a heart which is not strongly rotated about the longitudinal anatomic axis, the axis, $S\hat{A}_{QRS}$, is directed more posteriorly than $S\hat{G}$.[2] The lines drawn perpendicularly to the centers of the arrows representing the vectors should reach the body surface at the zero isopotential line. It will be observed that, on the front of the thorax, the point at which the perpendicular to the mean QRS touches the sur-

*This statement is based on the assumption that the polarized shells appearing within the myocardium are continuous, and that the intensity of polarization of each shell is the same at each part of the shell. Since there is good reason to believe that neither of these conditions obtains, the lines separating the regions in which the net QRS or QRS-T areas are of different sign do not represent accurately the projected boundaries upon the body surface of $S\hat{A}_{QRS}$ and $S\hat{G}$. The nearer the heart the surface point is, the greater the likelihood of error.

A second purpose of the experiments was to seek additional evidence for or against the earlier interpretation placed upon individual differences in the magnitude, A_{QRS}, that is, the manifest magnitude of the mean QRS axis recorded in the limb leads. If that magnitude is zero, $S\hat{A}_{QRS}$ (the mean spatial axis) should point directly backward, perpendicular to the frontal plane.[2] In one of our subjects (Fig. 4), A_{QRS} was only 1.4 units in magnitude, and its direction was about −133 degrees. In this case, very evidently, as the distribution of the fields demonstrates, the previously stated interpretation of small A_{QRS} values is confirmed. However, the A_{QRS} value in the subject shown in Fig. 3 was only 3.3 units. If the mean spatial QRS axis, $S\hat{A}_{QRS}$, in this subject is 11.5 units, which was estimated to be the average value, then the vector should project back to form a 73 degree angle with the frontal plane. That the backward projection is not so great is probably indicated by the surface potential distribution. This case gives us the first objective evidence for a possibility we had previously suspected, namely, that, in certain persons, and especially in deep-chested, pyknic persons, such as this one, less than an average fraction of the potential change produced by the heart may be transmitted to the limb leads. The greater volume of body tissue may act much like fluid accumulation in the tissues, or the depth of the chest, by producing a relative forward displacement of the dipoles (Bayley, Wilson[8]), may reduce the magnitude of both $\hat{A}_{QRS}$ and $\hat{G}$. In another paper, now in press, we will show that in such cases the form of the QRS complex, rather than the magnitude, $\hat{A}_{QRS}$, affords the better indication of the direction of the spatial vector, $\hat{A}_{QRS}$. The spatial gradient, $S\hat{G}$, is apparently likewise reduced for the same reasons. There is, of course, a third way of accounting for some small magnitudes of the vectors, namely, that the *net* electromotive force generated by the heart is much less than the average in some cases. The form of the QRS complexes suggests that this factor, if present in Fig. 3, is of secondary importance.

The Potential of the Common Terminal.—A series of papers have advanced evidence which is believed to demonstrate the invalidity of the Einthoven triangle method as applied in human electrocardiography. The last paper in the series gives reasons for doubting that the potential of the common terminal of Wilson remains nearly at zero throughout the cardiac cycle.[9] Since our work is based upon the assumption that the mean potential of the common terminal is zero, or at the potential of the mid-points of the dipoles for both QRS and QRS-T, it is necessary for us to meet the objection. Fortunately our results enable us to draw some conclusions.

No one will quarrel with the self-evident statement that the electromotive forces responsible for the potential changes we are studying are produced in the heart. Therefore, subject to a possible discrepancy described in the footnote on page 699, if the body could be imagined as cut into two parts, with the surface cuts made along the isopotential lines of the figures, the section should pass through the heart. Inspection of our figures shows that this expectation is met for the QRS complex in eight of our ten cases; in two cases both the QRS and QRS-T section might miss the ventricular base by a centimeter or two, and in one other case (Fig. 1) only the QRS-T might miss it. If this is not due to the factor mentioned in the footnote (p. 699), it may imply that the mean potential of the common terminal is slightly negative, thus causing an apparent increase in the extent of the positive field. If this conclusion were to be accepted, then it is obvious from the potential differences shown by the limb leads that the mean potential of the right arm must be strongly negative during

SUBJECT 10.—White man aged 26 years. No heart disease. $\hat{A}_{QRS}$, +83 degrees, magnitude, 7.8 units; Ĝ, +69 degrees, magnitude, 10 units. Similar to Fig. 2, but the bands, as expected from vector directions, are more transverse, and the zones of overlapping are relatively narrow. Excellent agreement between indication of backward projection of $\hat{A}_{QRS}$ and the electric fields.

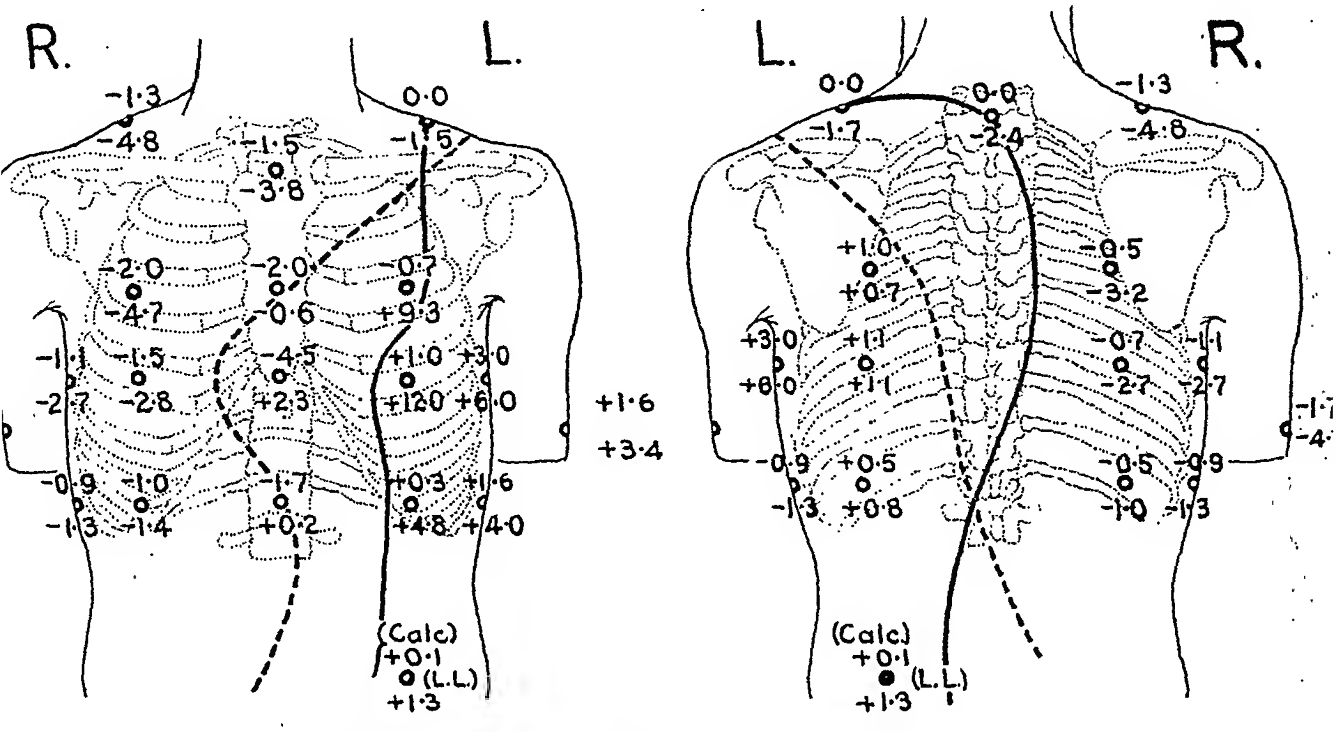

Fig. 3.—Subject 5. For interpretation, see Fig. 1.

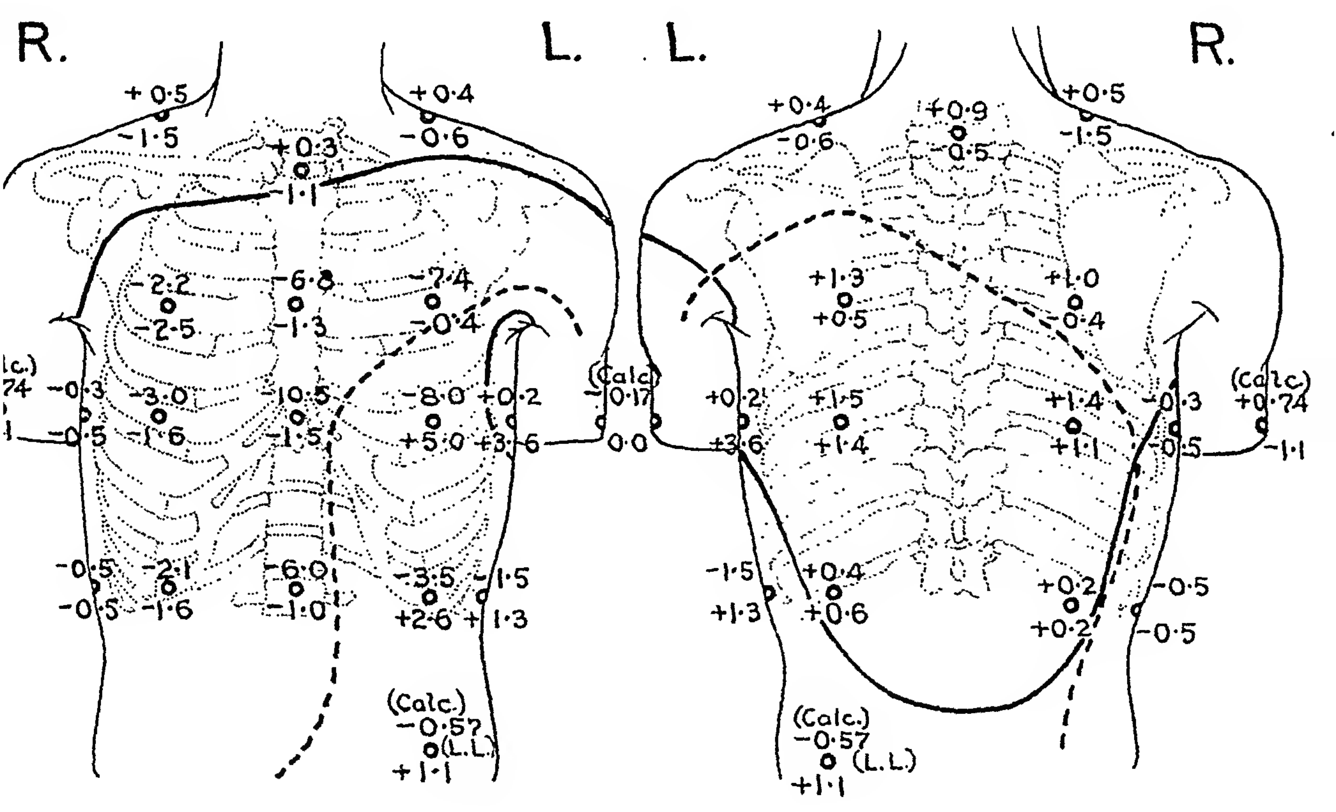

Fig. 4.—Subject 3. For interpretation, see Fig. 1.

DIPHTHERITIC MYOCARDITIS

With a Report of Two Cases

Major David Ball, M.C., Army of the United States

THE heart is often affected in diphtheria with resultant electrocardiographic changes. This paper is concerned with the changes occurring in adults only.

In this global war, many of our soldiers are stationed in areas where diphtheria is endemic amongst the native population. Some of our troops consequently develop diphtheria. It is the practice of this hospital (general hospital overseas) to take serial electrocardiograms on all cases of diphtheria throughout the course of the disease.

Twelve cases of diphtheria have been diagnosed and treated; electrocardiographic changes were found in two, an incidence of 16.5 per cent cardiac involvement. Eggleston[1] described T-wave changes (similar to this series) as the most frequently observed electrocardiographic alteration in 16 per cent of his cases. During the stage of inversion, the T-wave changes may so closely simulate the inverted "coronary T wave" of myocardial infarction that this error in diagnosis can be made unless attention is paid to the S-T interval.

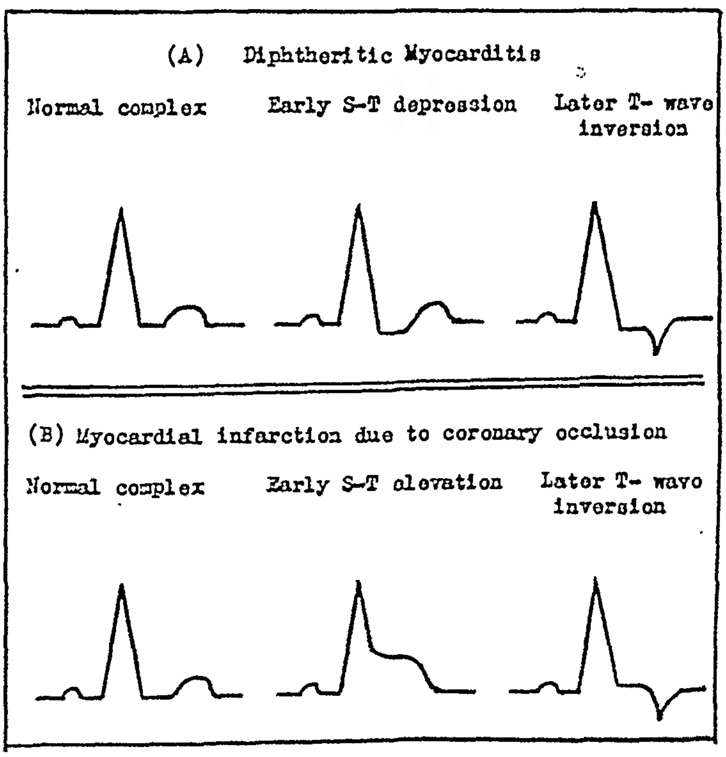

Fig. 1.—Schematic drawing illustrating the typical S-T and T-wave changes in (*A*) diphtheritic myocarditis and (*B*) myocardial infarction due to coronary occlusion.

The earliest electrocardiographic change observed in diphtheritic myocarditis (Fig. 1) is a depression of the S-T interval. The T wave then becomes lower in amplitude, isoelectric, diphasic, and finally inverted. The S-T interval always remains slightly depressed. This is in direct contrast to the S-T interval in myocardial infarction, where, after the initial marked elevation of the S-T interval and the subsequent inversion of the T waves, the S-T interval is always isoelectric or slightly above the isoelectric line.

Received for publication Sept. 25, 1944.

inscription of the QRS or QRS-T complexes. If, as the authors quoted believe, the right arm undergoes relatively little change in potential during the inscription of QRS, the positive fieldes shown by our diagrams should appear much smaller and the negative fields much larger. In no case was there evidence for this, although, obviously, minor discrepancies could not be recognized.

Our conclusion is that, with respect to the *mean* electrical axes, no "enormous error" can be introduced by the Einthoven triangle method. That there may be minor errors, especially when the heart is very horizontal, is likely, as a later paper will point out; but the errors in normal chests are nearly negligible practically, and can be allowed for in analysis. With respect to the initial *instantaneous* axes of the QRS complex, it is possible that the error may be greater.

SUMMARY

The distribution of the net QRS and QRS-T potentials on the body surface supports the earlier conclusion that there is a spatial angle between the mean spatial QRS axis ($S\hat{A}_{QRS}$) and the mean spatial QRS-T axis ($S\hat{G}$). The earlier inference that small magnitudes of the mean QRS axis are due to a relatively backward projection of the mean spatial QRS axis ($S\hat{A}_{QRS}$) also receives added support, but the results indicate that some other factor or factors are sometimes also involved. Our results suggest further that no very large errors are involved in the use of the common terminal of Wilson as a zero reference point.

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Feb. 13, 1944, five days after the appearance of a membrane, showed definite changes. There was a prompt response to antitoxin, the throat cleared rapidly, and the patient remained symptom free. Because of the electrocardiographic changes present, he was kept quietly in bed and serial electrocardiograms were taken (Fig. 2). At no time were there any complaints referable to the cardiovascular system, physical examination of the heart was negative, and blood pressure and x-ray of the chest were normal. The electrocardiogram was considered normal on June 1, 1944, three and a half months after the first change was detected. He was returned to duty, resumed normal activities, and has re-

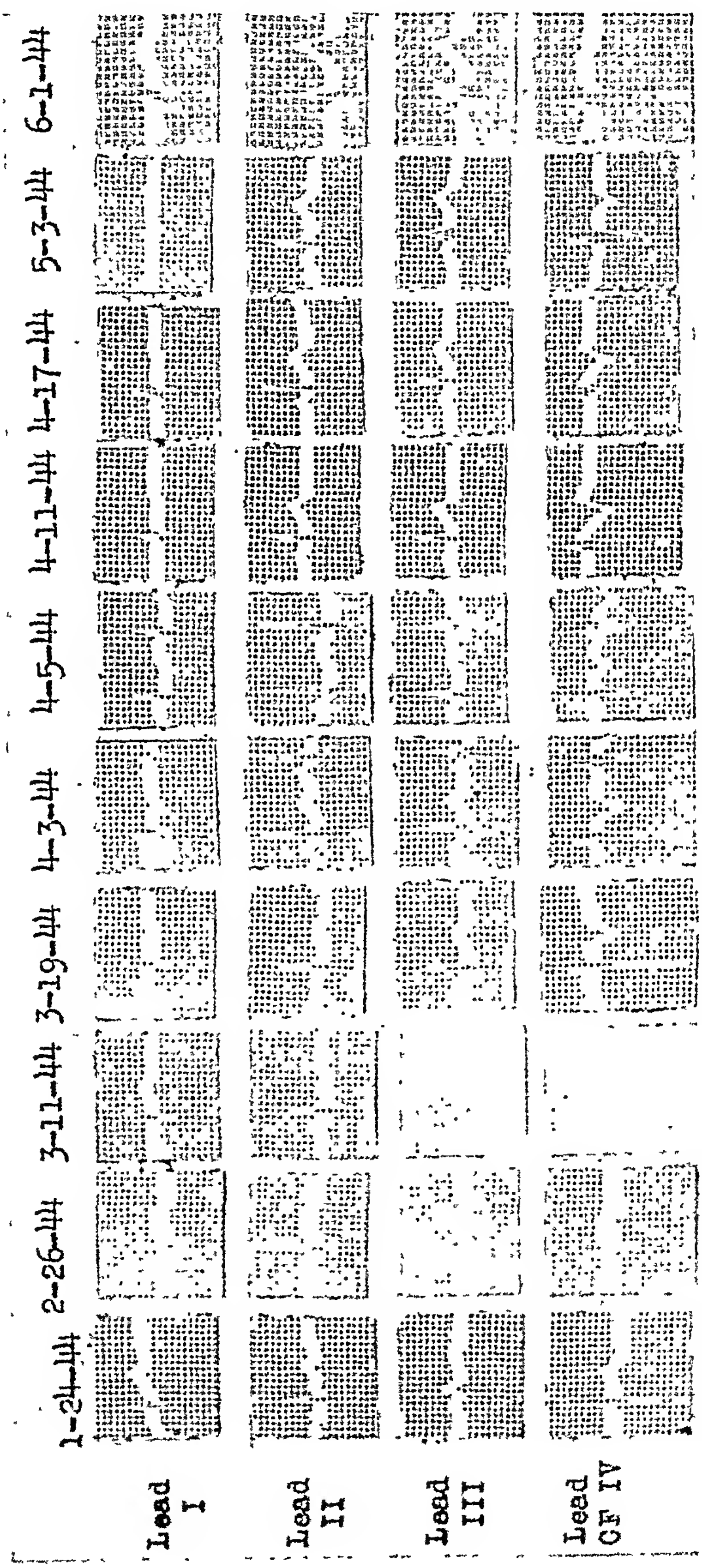

Fig. 2.—Case 2. Serial electrocardiograms, showing the typical changes of diphtheritic myocarditis in an adult with diphtheria.

REPORT OF CASES

CASE 1.—A man, aged 22 years, complained of a sore throat and generalized aches and pains four days before admission to the hospital. Physical examination revealed what appeared to be an acute follicular tonsillitis which responded promptly to sulfadiazine by mouth. Five days later, while convalescing, he developed a sore throat, headache, and temperature of 101.8° F. Throat culture was positive for Klebs-Löffler bacilli and 40,000 units of diphtheria antitoxin were administered. Electrocardiogram (Fig. 2) taken on

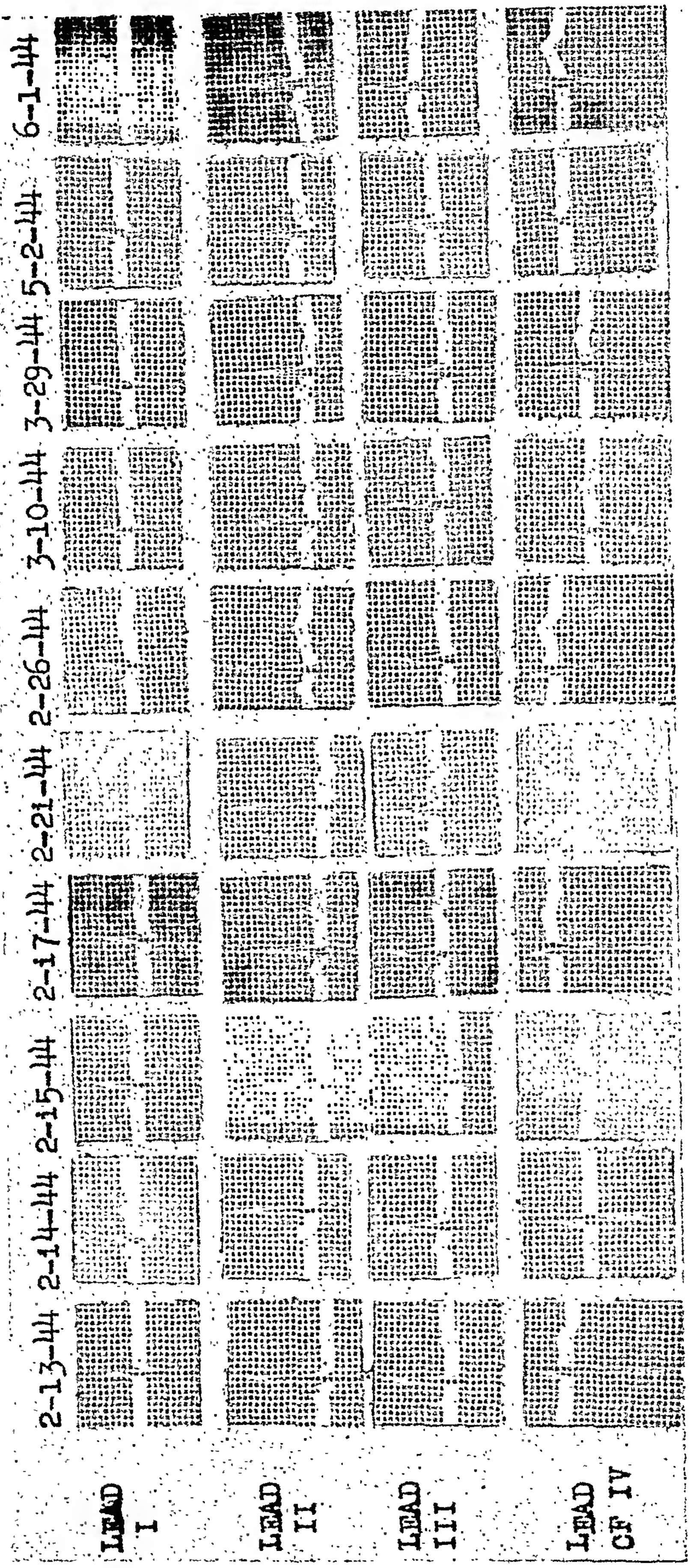

Fig. 2.—Case 1. Serial electrocardiograms, showing the typical changes of diphtheritic myocarditis in an adult with diphtheria.

THE USE OF THE AUGMENTED UNIPOLAR LEFT LEG LEAD IN THE DIFFERENTIATION OF THE NORMAL FROM ABNORMAL Q WAVE IN STANDARD LEAD III

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IN THE original descriptions of the electrocardiographic changes which follow localized myocardial injury[1] or coronary ligation in animals[2] and coronary occlusion in man,[3-5] emphasis was placed exclusively upon the changes in the ST-T segment. Although Q waves were present in the illustrations accompanying these reports, no comment was made regarding them, perhaps because of the known occurrence of Q_3 normally.[6-11] Passing mention was made of the presence of Q_3 in myocardial infarction by several authors during the next decade,[12-14] but the diagnostic significance was not appreciated until the work of Pardee,[15] in 1930. He concluded that a Q wave in Lead III which was 25 per cent or more of the tallest R wave in any of the three standard leads was of clinical significance, in curves which did not show right axis deviation, because of its frequent association with coronary artery disease and its rarity among normal persons. His observations were soon confirmed by others,[16-22] who found that a very high percentage of the electrocardiograms showing a Q_3 which conformed to Pardee's criteria or to slight modifications thereof was from patients with abnormal hearts, and a very small percentage was from persons with normal hearts. More recent studies, notably those of Short,[23] Stewart and Manning,[24] and Graybiel, et al.,[25] have indicated that a Pardee type of Q_3 which is indistinguishable from that associated with old posterior infarction is not infrequent in electrocardiograms from normal persons. It would thus appear that some additional method is needed for differentiating the Q_3 which often persists as a residue of old posterior infarction from the Q_3 which sometimes occurs normally.

Semidirect precordial leads, first described by Wolferth and Wood,[26] in 1932, but in use simultaneously by Wilson and his co-workers,[27] have aided greatly in the diagnosis of anterior infarction; they reveal many small infarcts that do not produce recognizable changes in the standard leads. Through the use of multiple precordial leads, Wilson, et al.,[27] in 1933, first advanced the explanation for the origin of the Q wave in myocardial infarction which is now generally accepted. They likened an infarcted area to a window or orifice in the ventricular wall through which potentials within the ventricular cavity are transmitted to the surface of the body. When the infarct is located in the anterior wall of the left ventricle, the potentials of the cavity are transmitted to the precordium and sometimes to the left arm, giving rise to abnormal Q and T waves in semidirect leads over the left ventricle, and sometimes in Lead I, as well. When the infarct is located in the posterior wall, abnormal Q and T waves appear in Leads II and III.

Semidirect esophageal leads provide a method for the study of lesions of the posterior wall which is comparable to the precordial leads for anterior wall lesions. An esophageal electrode was devised by Lieberson and Liberson,[28] and was applied by Hamilton and Nyboer[29] to the study of posterior infarction. Ac-

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Received for publication Sept. 25, 1944.

mained symptom free. It cannot be stated with certainty whether or not this patient had diphtheria when he was first admitted to the hospital with what appeared to be an acute follicular tonsillitis. In view of the fact that there were other cases of diphtheria in the hospital at the time, it is possible and likely that the first evidence of "sore throat" was due to diphtheria.

CASE 2.—A man, aged 37 years, was admitted to the hospital on Jan. 24, 1944, with nasopharyngitis. A routine electrocardiogram was normal. While convalescing, he developed a perianal cellulitis, secondary to an internal hemorrhoid. This was treated conservatively. On Feb. 19, 1944, he had an epistaxis. Five days later (Feb. 24, 1944) he complained of a sore throat and the next day was found to have a dirty, gray membrane in the left nostril and an early membrane formation on both tonsils. Temperature was 102.6° F. A clinical diagnosis of diphtheria was made, nose and throat cultures were taken, and the patient was transferred to the isolation service and given 40,000 units of diphtheria antitoxin, intramuscularly. Nose and throat cultures were positive for Klebs-Löffler bacilli. The first electrocardiogram, taken Feb. 27, 1944, two days after the appearance of the membrane, was normal (Fig. 3). Temperature became normal on March 2, 1944, and the membrane disappeared on March 5, 1944. Nose and throat cultures, taken on March 9, and March 11, 1944, were still positive. A small follicle appeared on the left tonsil on March 12, 1944, and another dose of diphtheria antitoxin, 40,000 units, were given intramuscularly. An electrocardiogram, taken the next day, sixteen days after the appearance of a membrane, showed the first deviation from the normal, a depression of the S-T interval in Lead I and elevation in Lead IV. Electrocardiogram, taken on March 19, 1944, showed typical changes seen in diphtheritic myocarditis. The only clinical cardiac finding at this time was a persistent tachycardia with a rate of 120 per minute. Blood pressure was 120/70 and teleroentgenogram was normal. The patient then developed a classical, marked peripheral neuritis in all extremities with marked motor weakness. Marked apprehension and nervousness were present, and there was beginning weight loss. The nervousness, tachycardia, and weight loss suggested the clinical picture of hyperthyroidism. Unfortunately, there was no machine available to determine the basal metabolic rate. The patient was given a therapeutic test with lugol solution and, within a week, the pulse rate was normal, nervousness disappeared, and appetite returned. Lugol's solution was administered for another ten days and then discontinued. Serial electrocardiograms (Fig. 3) show the typical changes observed in this case with a return to an almost normal curve. The peripheral neuritis gradually improved and the patient was able to walk and get around before being evacuated to the zone of the interior.

COMMENT

The electrocardiographic changes observed in both cases described would indicate that there was severe and extensive myocardial involvement. At no time did these patients have any complaints referable to the cardiovascular system and, at no time, were there any clinical findings to suggest involvement of the heart. In both cases, the changes were reversible and shifting from day to day, suggesting that the changes observed are "toxic" in origin and not due to any structural damage to the heart muscle.

CONCLUSIONS

1. The electrocardiographic changes observed in two cases of diphtheria in adults are described. These changes conform to a type that is easily differentiated from those observed in myocardial infarction due to coronary artery occlusion.
2. The S-T interval is always depressed in diphtheritic myocarditis.
3. The changes are reversible and "shifting."
4. These effects are probably toxic in origin in diphtheritic myocarditis.
5. There was no clinical evidence of heart disease in either case described.

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Throughout this study, the Cambridge string galvanometer was used. Esophageal leads were taken with the subject in the recumbent position, using an improvised electrode made by passing a thin, insulated, braided copper wire through a Rehfuss tube, the tip of which served satisfactorily as a contact. The tube was marked off in 2.5 cm. segments, and an ordinary battery clamp was used as the contact at the proximal end. The tip could be readily passed nasally, and the procedure was not accompanied by any notable trauma. The indifferent electrode for the esophageal leads was the same as for the unipolar extremity and precordial leads. Our tracings agree very well with those of Nyboer,[30] and we have accepted his values of 35 to 40 cm. from the nares as the level of the auricles, and 45 to 55 cm. as the ventricular levels. In recording the measurements of the deflections, correction was made for errors in standardization.

PRESENTATION AND DISCUSSION OF RESULTS

A. *Mode of Establishing the Diagnosis.*—

1. Cases of Posterior Myocardial Infarction: A diagnosis of posterior infarction was made in a total of twenty-five cases (Table I). Four of these patients had a recent posterior infarct, as revealed by the electrocardiogram and confirmed at autopsy (Cases 13, 14, 16, and 19). Each of the remaining twenty-one patients had an old posterior infarct. Ten had been under our care during the acute attack months or years previously (Cases 2, 8, 20, 21, 22, 27, 31, 32, 46, and 47), at which time the classical signs were demonstrated in serial electrocardiograms. In addition, esophageal leads, taken at the time of this study, confirmed the presence of the old posterior infarct in all ten cases. The diagnosis was established in the other eleven cases (Cases 4, 6, 10, 12, 23, 24, 25, 35, 48, 49, and 50) by means of esophageal leads.

A summary of the esophageal lead data is given in Table I. According to Nyboer,[30] a Q_{EV} that exceeds 0.4 mv. is diagnostic of posterior infarction, especially if it is relatively large in proportion to the R wave in Lead E_V. Q_{EV} was 0.4 mv. or more in twenty of the twenty-two cases in this group in which esophageal leads were taken. The two remaining patients (Cases 10 and 48) showed Q waves in the esophageal leads which were less than 0.4 mv. in depth, measuring

TABLE I. ELECTROCARDIOGRAPHIC MEASUREMENTS IN TWENTY-FIVE CASES OF POSTERIOR INFARCTION

QRS	Q_2			Q_3			$\%Q_3$	Q_{aVF}			Q_{EV}			DURATION OF
DUR^N.	DUR^N.	VOLTAGE	$\%R_2$	DUR^N.	VOLTAGE	$\%R_3$	TALLEST R	DUR^N.	VOLTAGE	$\%R_{aVF}$	DUR^N.	VOLTAGE	$\%R_{EV}$	INFARCT
0.09	0.02	0.1	8	0.03	0.7	235	55	0.03	0.4	100	0.03	0.9	85	1 1/2 YEARS
0.08	—	—	—	0.04	0.9	225	55	0.02	0.45	110	0.03	0.6	40	3 MONTHS
0.08	0.01	0.1	15	0.02	0.35	70	65	0.02	0.3	60	0.05	0.55	INF.	OLD
0.10	0.03	0.1	30	0.05	0.4	INF.	60	0.03	0.25	200	0.03	0.4	100	2 YEARS
0.10	0.02	0.1	20	0.03	0.5	500	80	0.03	0.3	INF.	0.03	0.3	35	1 YEAR
0.08	0.02	0.1	10	0.03	0.7	175	55	0.03	0.3	60	0.03	0.7	INF.	2 MONTHS
0.07	0.02	0.15	100	0.04	0.9	200	100	0.03	0.5	125	ESOPHAGEAL LEADS NOT DONE			2 DAYS
0.09	0.03	0.1	100	0.02	0.15	INF.	50	0.02	0.1	135	ESOPHAGEAL LEADS NOT DONE			1 MONTH
0.14	—	—	—	0.04	1.0	INF.	90	0.04	0.7	INF.	ESOPHAGEAL LEADS NOT DONE			1 MONTH
0.07	0.02	0.3	60	0.03	0.8	INF.	80	0.03	0.4	INF.	0.04	1.5	500	2 WEEKS
0.10	0.03	0.4	90	0.03	0.7	200	160	0.03	0.6	120	0.02	0.55	45	7 MONTHS
0.11	0.02	0.3	85	0.03	0.55	200	75	0.03	0.4	200	0.04	0.7	70	1 1/2 YEARS
0.08	0.01	0.3	75	0.03	0.5	150	85	0.02	0.35	100	0.02	0.5	135	14 MONTHS
0.08	0.03	0.2	135	0.04	0.75	INF.	100	0.03	0.5	INF.	0.03	0.55	1100	OLD
0.11	0.02	0.2	45	0.05	1.1	275	80	0.05	0.5	200	0.02	0.45	100	OLD
0.09	0.02	0.3	30	0.03	0.55	60	55	0.03	0.4	42	0.03	0.85	35	1 YEAR
0.10	0.02	0.65	90	0.02	0.5	70	65	0.02	0.65	80	0.02	0.7	55	1 1/2 YEARS
0.07	0.02	0.1	15	0.02	0.4	INF.	40	0.02	0.3	INF.	0.03	1.0	100	8 MONTHS
0.08	0.03	0.5	125	0.03	0.8	400	100	0.03	0.8	400	0.04	1.4	1400	8 MONTHS
0.08	—	—	—	0.04	0.9	INF.	112	0.03	0.8	1600	0.03	0.8	INF.	OLD
0.07	—	—	—	0.02	0.3	100	25	—	—	—	0.03	0.6	100	13 MONTHS
0.11	—	—	—	0.04	0.6	INF.	60	—	—	—	0.03	1.7	115	10 MONTHS
0.07	0.04	0.25	INF.	0.04	0.4	INF.	135	0.04	0.2	INF.	0.03	0.25	75	7 MONTHS
0.07	0.02	0.35	40	0.035	0.55	85	50	0.025	0.4	35	0.03	0.9	55	7 MONTHS
0.10	—	—	—	—	—	—	—	—	—	—	—	—	—	OLD

cording to Nyboer,[30] a Q deflection in esophageal leads at the ventricular level (Lead E_V) is indicative of posterior infarction if it has a value of 0.4 mv. or is large in proportion to the R wave in Lead E_V.

Although esophageal leads are valuable, the procedure is unpleasant; if the patient is acutely ill, it may be dangerous. For these reasons, esophageal leads have not met with extensive clinical application.

In 1934, Wilson, et al.,[31, 32] presented a unique method of obtaining extremity potentials which were *unipolar*. They also made the significant observation that posterior infarctions usually face toward the left hind leg in the dog, and toward the left leg in man. Hamilton and Nyboer[29] and Kossmann and de la Chapelle[43] also noted that the electrocardiographic changes of posterior infarction may appear not only in Lead III and in esophageal leads from the ventricular level, but also in the left leg unipolar lead.

Goldberger[33] simplified Wilson's technique of obtaining unipolar precordial leads and also devised a method of augmenting by one and one-half times the hitherto small unipolar extremity potentials. He stated[34, 35] that small posterior infarctions may be shown by the left leg unipolar lead when there are no changes in the standard leads.

In a paper published after the completion of our study, Lyle[36] utilized the unipolar left leg potential of Wilson as a means of differentiating the normal Q_3 from that associated with posterior infarction. She studied twenty-nine cases in which there was a deep Q wave in standard Lead III and found that all ten patients who gave a history of coronary occlusion had a large Q wave in Lead V_F. She stated that it would be necessary to study a much larger number of cases to ascertain the normal limits of the Q wave in Lead V_F and to obtain conclusive statistical evidence of the diagnostic significance of the QRS pattern in this lead. The data presented in this communication provide further evidence bearing on this problem.

METHOD AND MATERIAL

Forty-nine persons with prominent Q or QS waves in Lead III were selected for study. In forty-five of the cases the electrocardiograms conformed to the criteria of Pardee:[15] (1) Q_3 was at least 25 per cent of the largest R in any of the three standard leads, (2) right axis deviation was not present, and (3) S_3 was absent. In a few of the cases, QRS_3 was represented by a QS complex rather than a QR complex, as originally specified by Pardee. In many of these cases it was difficult or impossible to express a definite opinion from the standard leads alone as to whether or not an old posterior infarct was present. One of the four remaining subjects (Case 15) had a prominent Q_3, together with right axis deviation resulting from pulmonary embolism. The other three subjects were controls with right axis deviation due to a vertical position of the heart, and had a Q_3 which ranged from 20 per cent to 33 per cent of the tallest R in the standard leads. One additional subject (Case 50) showed an RS complex instead of a Q wave in Lead III, but was included in the study because of ST-T changes typical of posterior infarction.

In all fifty cases, the following leads were taken: the three standard leads of Einthoven, six unipolar precordial leads (V_1 to V_6, inclusive), using the technique of Wilson, et al.,[37] or Goldberger,[33] and three augmented unipolar extremity potentials, according to the technique of Goldberger.[34]* The presence or absence of posterior infarction was positively established either by autopsy or by esophageal leads, supported by clinical data which in many cases included previous electrocardiograms. The electrical position of the heart was ascertained from the precordial and unipolar extremity potentials, using Wilson's[37] criteria.

*Goldberger's modification differs from Wilson's original central terminal only by the absence of the 5,000-ohm resistances. Precordial leads obtained by these two methods on the same patients were indistinguishable from one another; the two electrodes were completely interchangeable for this purpose, so far as we could ascertain. The advantage of the Goldberger electrode is that it can be used either for recording the unipolar precordial potentials or the augmented unipolar extremity potentials, whereas the original Wilson electrode does not lend itself to the latter.

the esophageal leads and also in Leads II, III, and aV_F. The diagnosis was confirmed at autopsy. Case 38 (Fig. 2) was a representative normal control having a prominent Q wave in Lead III but no signs of infarct in the esophageal leads or in Lead aV_F.

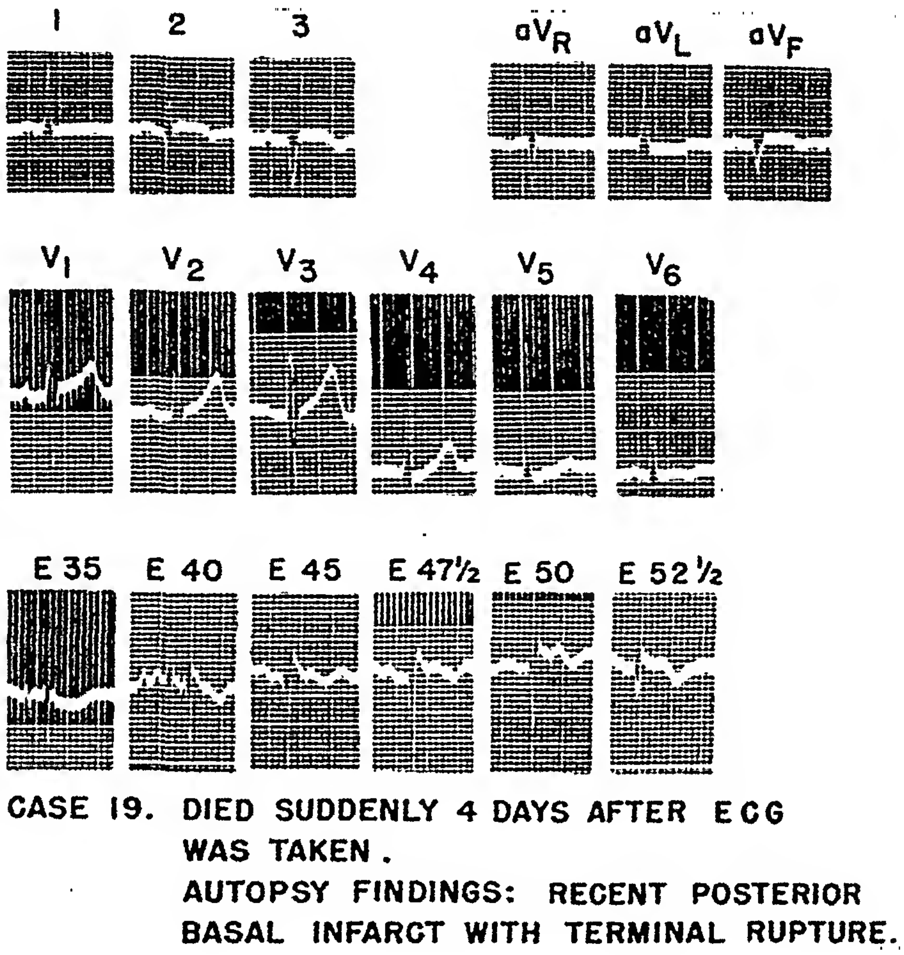


Fig. 1.

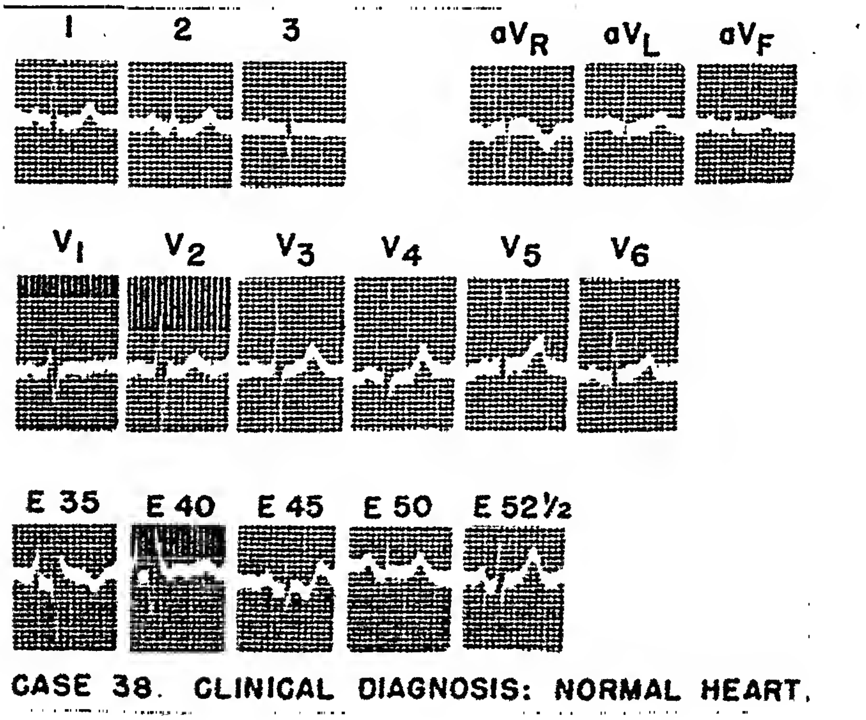


Fig. 2.

0.3 and 0.25 mv., respectively. However, when the amplitude of Q_{EV} was considered in relation to R_{EV}, the ratios were 35 per cent and 75 per cent, respectively. In all of the remaining twenty cases in this group in which esophageal leads were made, Q_{EV} was also more than 25 per cent of R_{EV}, suggesting that this may be a more valuable criterion than the actual voltage of Q_{EV}.

2. Cases in Which There Was No Posterior Infarction: Posterior infarction was excluded in a total of twenty-five cases (Table II)—in three by autopsy and in the other twenty-two by esophageal leads. Q_{EV} was absent in sixteen of the twenty-two cases in which esophageal leads were classed as negative. In five cases (Cases 26, 30, 37, 42, and 43), Q_{EV} was considered insignificant because it was less than 0.4 mv. in amplitude and less than 25 per cent of R_{EV}. In the remaining case (Case 41), Q_{EV} was 0.6 mv. in amplitude, but was not considered a remnant of infarction because it was followed by an R_{EV} which measured 2.4 millivolts. The history was negative for coronary thrombosis in all but one of the cases in which posterior infarction was excluded by esophageal leads. The sole patient with a positive history (Case 42) was under our care during the acute attack, at which time serial electrocardiograms were diagnostic of anteroseptal infarction. Six months later, at the time of this study, electrocardiographic evidence of this infarct had completely disappeared. A small Q and a large R wave in Leads II and III, due to vertical position of the heart, were present in all electrocardiograms in this case, but posterior infarction was excluded by the absence of serial changes in QRS-$T_{2 \text{ and } 3}$ and by negative esophageal leads.

The difference in the esophageal lead pattern associated with posterior infarction and that in uninfarcted controls is illustrated by Figs. 1 and 2. Case 19 (Fig. 1) had typical electrocardiographic signs of posterior infarction in

TABLE II. ELECTROCARDIOGRAPHIC MEASUREMENTS IN TWENTY-FIVE CASES IN WHICH THERE WAS NO POSTERIOR INFARCTION

	Q_2			Q_3			$\%Q_3$	Q_{AVF}			Q_{EV}			
DUR^N.	DUR^N.	VOLT.	$\%R_2$	DUR^N.	VOLT.	$\%R_3$	TALLEST R	DUR^N.	VOLT.	$\%R_{AVF}$	DUR^N.	VOLT.	$\%R_{EV}$	COMMENT
0.11	—	—	—	0.02	1.1	185	65	—	—	—	—	—	—	SEMIHORIZONTAL HEAR
0.10	—	—	—	0.04	0.8	400	55	—	—	—	—	—	—	" "
0.08	—	—	—	0.02	0.45	200	45	—	—	—	—	—	—	" "
0.06	—	—	—	0.03	0.9	INF.	45	—	—	—	—	—	—	" "
0.08	—	—	—	0.03	0.3	100	25	—	—	—	—	—	—	" "
0.09	—	—	—	0.02	0.5	250	60	—	—	—	—	—	—	" "
0.08	—	—	—	0.02	0.7	80	70	0.02	0.15	20	ESOPHAGEAL LEADS NOT DONE			NO INFARCT. PULMONA EMBOLI (AUTOPSY)
0.09	—	—	—	0.02	0.7	1400	120	—	—	—	ESOPHAGEAL LEADS NOT DONE			NO INFARCT. L.V. HY TROPHY. PULMONARY EMBOLI (AUTOPSY)
0.11	—	—	—	0.03	0.75	INF.	100	—	—	—	ESOPHAGEAL LEADS NOT DONE			NO INFARCT. L.V. HY TROPHY. DIFFUSE FIE SIS (AUTOPSY)
0.08	0.02	0.1	40	0.03	0.6	300	60	0.02	0.13	40	0.03	0.2	22	SEMIHORIZONTAL HEAR
0.07	—	—	—	0.03	0.65	INF.	55	—	—	—	—	—	—	" "
0.06	0.02	0.1	25	0.02	0.3	300	60	0.02	0.2	65	—	—	—	POSTURAL Q_3, WITH (
0.07	—	—	—	0.02	0.3	35	25	—	—	—	0.02	0.2	12	SEMIVERTICAL HEART
0.08	—	—	—	0.03	1.0	300	60	—	—	—	—	—	—	SEMIHORIZONTAL HEAR
0.08	—	—	—	0.03	0.45	INF.	150	—	—	—	—	—	—	" "
0.08	—	—	—	0.03	0.4	400	60	—	—	—	—	—	—	" "
0.07	—	—	—	0.03	0.5	250	70	—	—	—	0.02	0.2	11	" "
0.06	—	—	—	0.02	0.4	200	45	—	—	—	—	—	—	" "
0.06	—	—	—	0.02	0.6	INF.	65	—	—	—	—	—	—	" " EARLY L.V. HYPERTRO
0.10	—	—	—	0.03	0.45	250	55	0.02	0.13	16	—	—	—	SEMIHORIZONTAL HEAR
0.08	0.02	0.45	20	0.02	0.55	26	23	0.01	0.6	25	0.02	0.6	25	VERTICAL HEART
0.10	0.01	0.15	15	0.03	0.45	33	33	0.02	0.2	17	0.02	0.2	8	VERTICAL HEART. OL ANTEROSEPTAL INFARC
0.08	0.01	0.1	8	0.02	0.3	20	20	0.02	0.2	14	0.02	0.3	12	VERTICAL HEART
0.12	—	—	—	0.06	0.7	2800	100	—	—	—	—	—	—	L.B.B.B. NO INFARC
0.10	—	—	—	0.04	1.4	700	85	0.03	0.85	850	—	—	—	MARKED RESP. VARIAT L.V. HYPERTROPHY

that the two groups of cases cannot be differentiated on the basis of the depth of Q_3 or its relation to the tallest R wave.

2. Occurrence of Q_2 and Its Relation to R_2: A significant Q_2 (greater than 25 per cent of R_2, according to Durant[21]) was present in thirteen of the twenty-five patients with posterior infarction (Table I) and was found in only two of the twenty-five persons without infarction. Admittedly, this is a helpful finding when it does appear, but it is important to note that it was absent in nearly half of our patients with posterior infarction.

3. The Duration of Q_3: According to Bayley,[33] the duration of Q_3 is more important than its amplitude or its relation to the tallest R wave in the standard leads; his criterion for an abnormal Q_3 was a duration of 0.04 seconds or more.

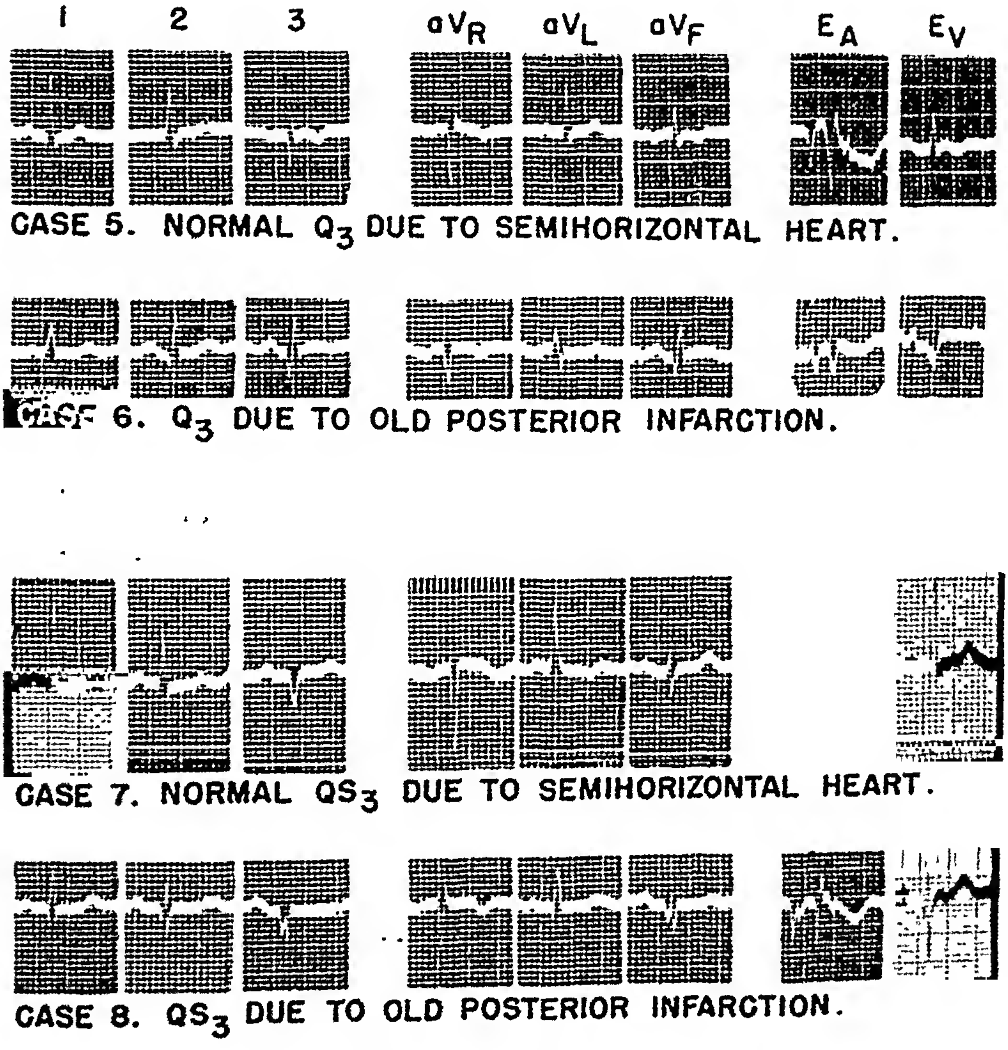


Fig. 1.—Use of augmented unipolar left leg potential (Lead aV_F) to differentiate the normal Q_3 from that due to posterior infarction.

Only nine (Cases 4, 8, 10, 13, 16, 23, 35, 47, 48) of our twenty-five patients with posterior infarction fulfilled this criterion (Table I). On the other hand, three (Cases 3, 44, 45) of the twenty-five subjects with Q_3 but without posterior infarction also met the same requirement. Each of these cases had clinical and electrocardiographic signs of left ventricular hypertrophy. However, Graybiel, et al.,[22] have demonstrated a prolonged Q_3 in apparently normal aviators.

From the foregoing it is evident that neither the depth of Q_3 in relation to the tallest R, the duration of Q_3, nor the ratio of Q_2 to R_2 is entirely dependable for determining the presence or absence of old posterior infarction.

B. *Comparison of Standard Leads of Posterior Infarction With Those of Uninfarcted Controls.*—

1. Depth of Q_3 and Its Relation to the Tallest R: Measurements of the voltage of Q_3 and a ratio of the amplitude of Q_3 to that of the tallest R are recorded in Table I for the cases of posterior infarction and in Table II for the uninfarcted controls. Q_3 was 25 per cent or more of the tallest R in twenty-four of the twenty-five cases of posterior infarction, and varied in

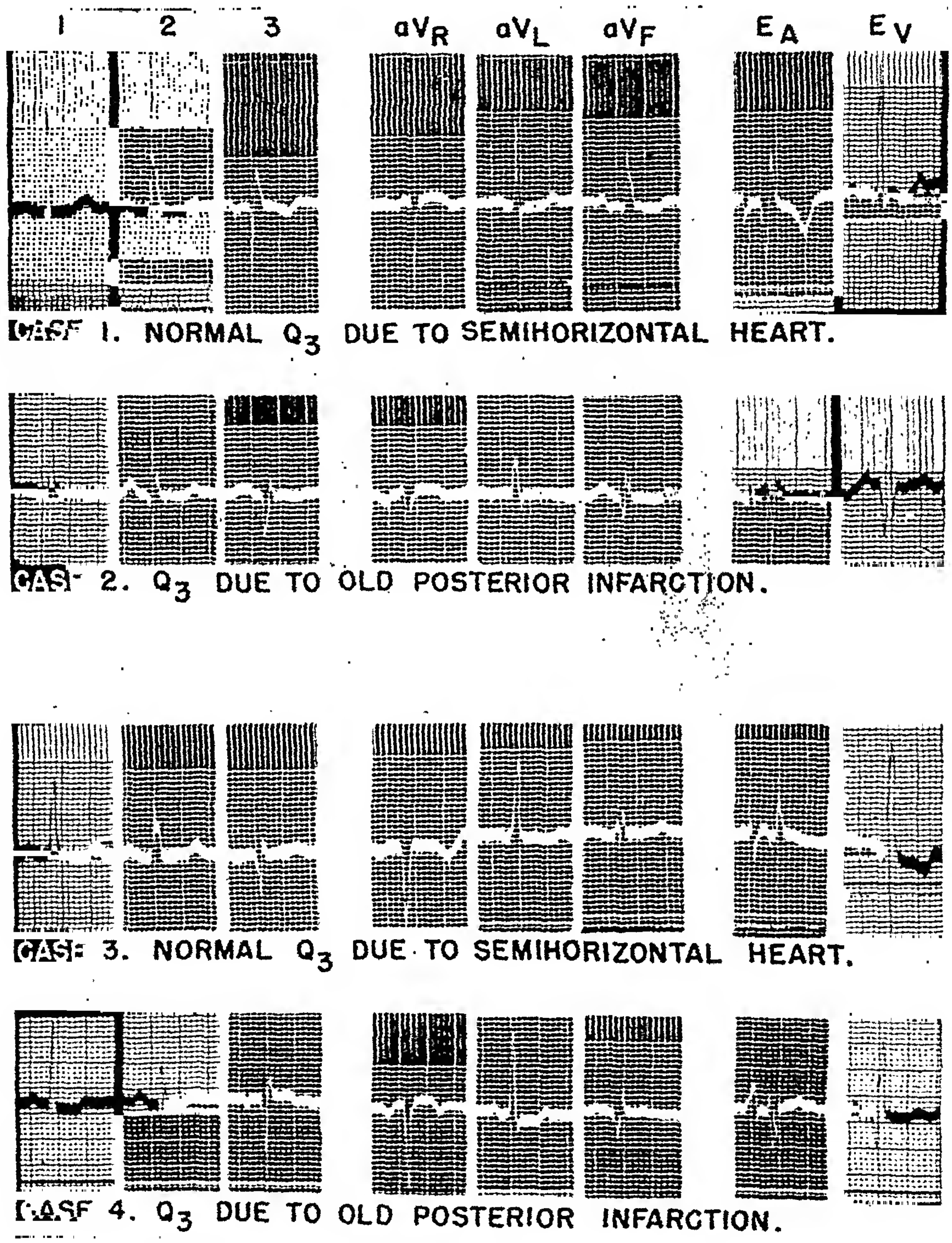


Fig. 3.—Use of augmented unipolar left leg potential (Lead aV_F) to differentiate normal Q_3 from that due to posterior infarction.

depth from 0.15 to 1.1 millivolts. However, in all but two of the twenty-five persons without posterior infarction, Q_3 was entirely comparable, ranging from 0.3 to 1.4 mv. and amounting to 25 per cent or more of the tallest R wave. In the two exceptions (Cases 41 and 43) the ratio was borderline, being 23 per cent and 20 per cent, respectively. It is thus evident

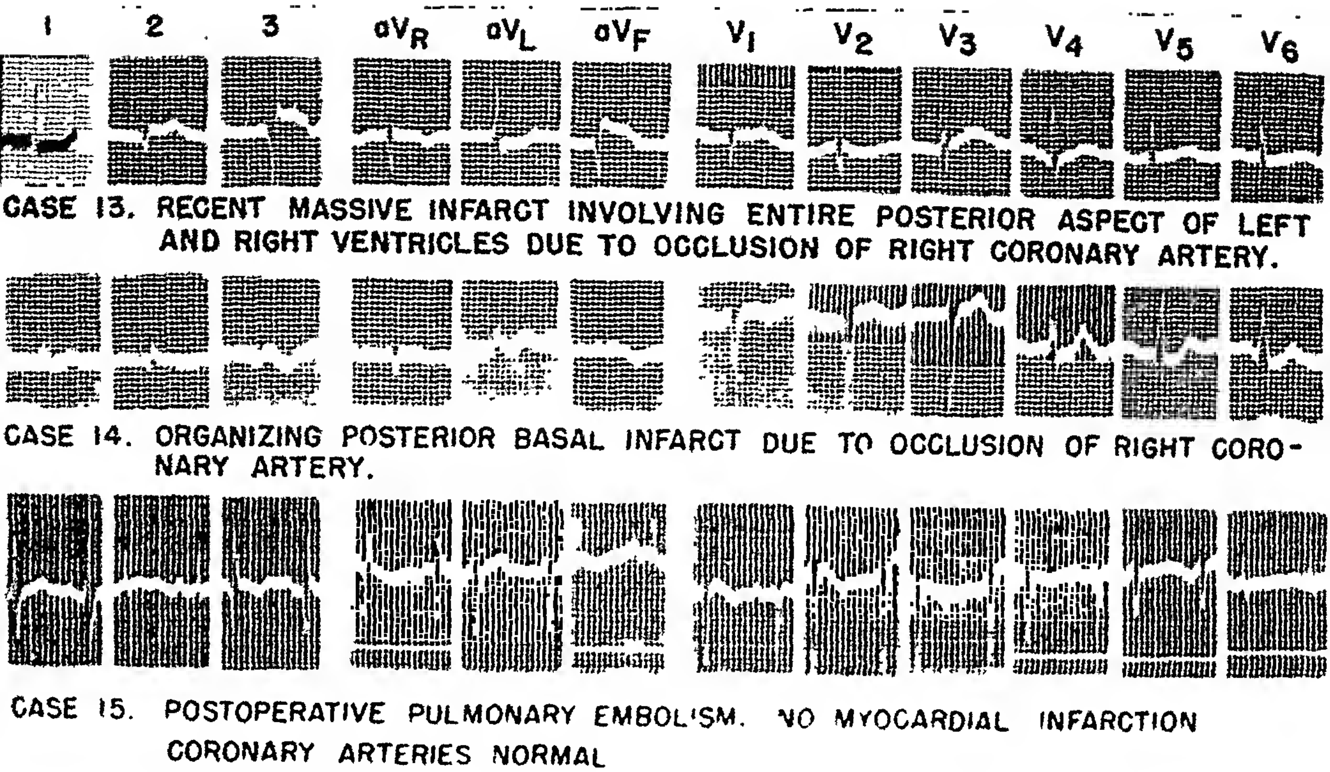


Fig. 6.—Cases with autopsy confirmation.

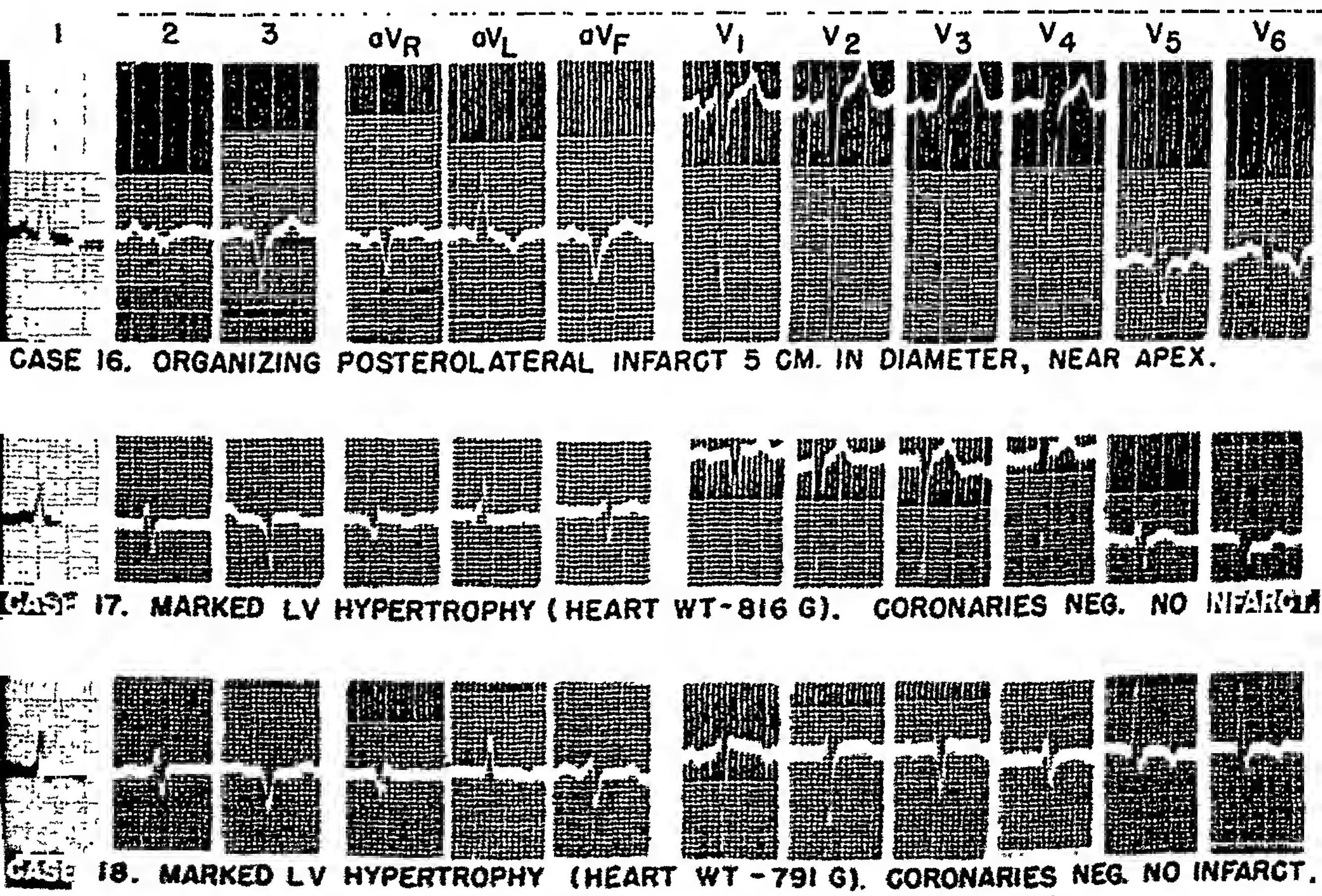


Fig. 7.—Cases with autopsy confirmation.

In Figs. 3, 4, and 5, electrocardiograms of six patients with proved posterior infarction (Cases 2, 4, 6, 8, 10, and 12) are paired off for purposes of comparison with the electrocardiograms of six subjects in whom the diagnosis of posterior infarction was excluded (Cases 1, 3, 5, 7, 9, and 11). The QS_3 type of complex described by Durant[21] is represented in Cases 7 and 8; the QR complex of Pardee,[15] in the remainder. Attention is directed to the close resemblance of the standard leads of each pair of cases. Comparison of Q_3 of the even-numbered cases, in which the presence of posterior infarction was established, with the corresponding odd-numbered cases, in which it was excluded, reveals no significant difference in the duration of Q_3, in its absolute voltage, or in its amplitude relative to the tallest R in the standard leads. On the other hand, comparison of the QRS complexes in Lead aV_F of each pair of cases reveals significant differences in contour which permit a sharp differentiation between the infarcted and the control cases.

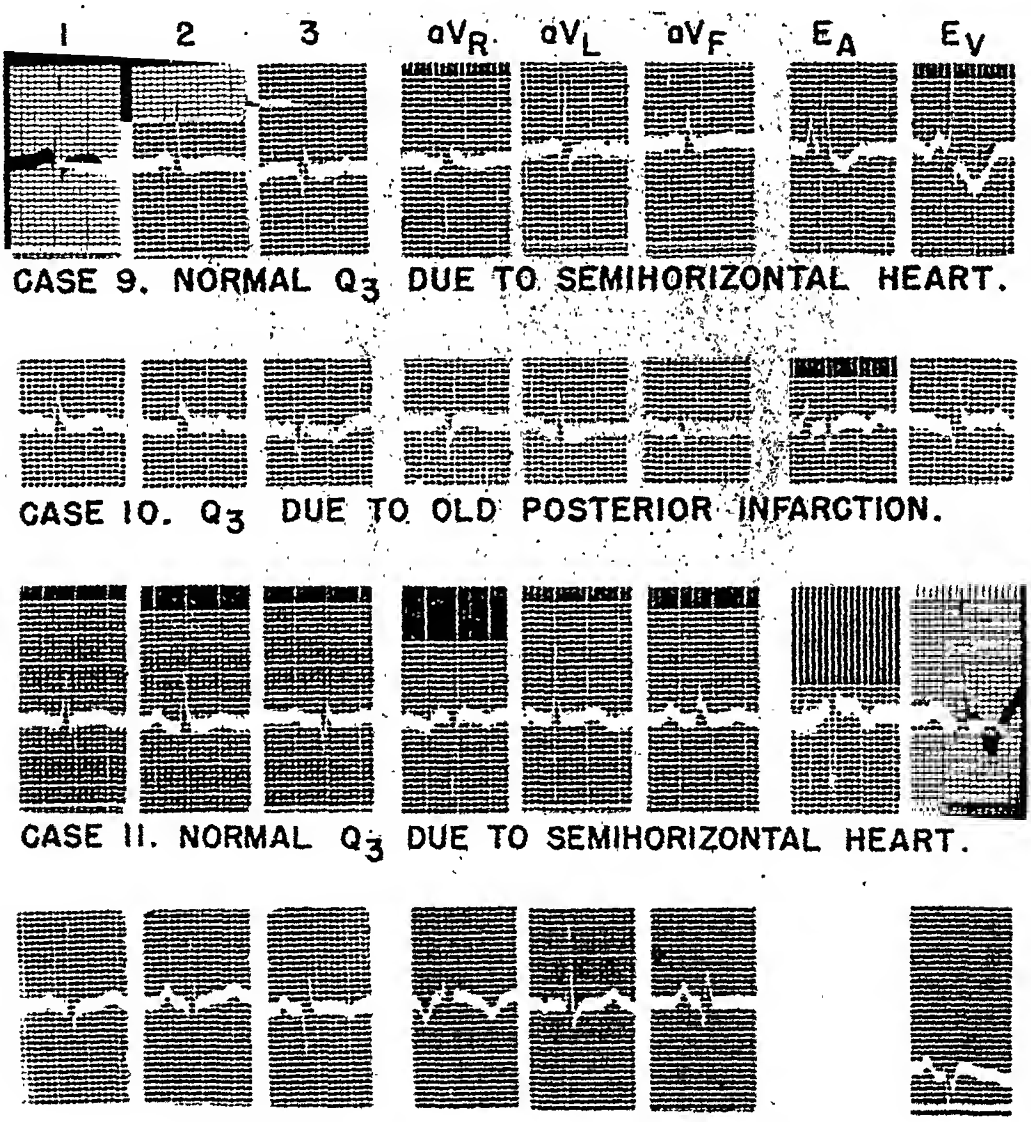


Fig. 5.—Use of augmented unipolar left leg potential (Lead aV_F) to differentiate normal Q_3 from that due to posterior infarction.

Further comparisons are afforded by Figs. 6 and 7, which illustrate cases in which the diagnosis was established by autopsy. Fig. 6 includes a classical recent posterior infarct (Case 13), a case which is less typical, partly because of low voltage (Case 14), and a control (Case 15) which had a QRS-T complex suggestive of posterior infarction in Lead III but not in Lead aV_F. From this, together with the right axis deviation in the standard leads and the inversion of the T wave in the precordial leads over the right ventricle, the correct diag-

tracings, however, a small initial R wave was present.* The fact that the unipolar extremity leads showed horizontal position of the heart suggests that a portion of the right ventricle as well as the left may have been directed against the diaphragm, and therefore may have contributed to the pattern in Lead aV_F. The activation of this portion of the right ventricle may account for the small initial R wave which appeared in Lead aV_F and was carried over into Lead III.

A measurable QaV_F occurred in eight of the twenty-five persons without posterior infarction (Table II). It is therefore evident that the mere presence of a Q wave in Lead aV_F does not necessarily indicate the existence of a posterior infarct. Since all twenty-five of these control subjects had prominent Q waves in Lead III, it is obvious that QaV_F is a much less common finding than Q_3 in the absence of infarction.

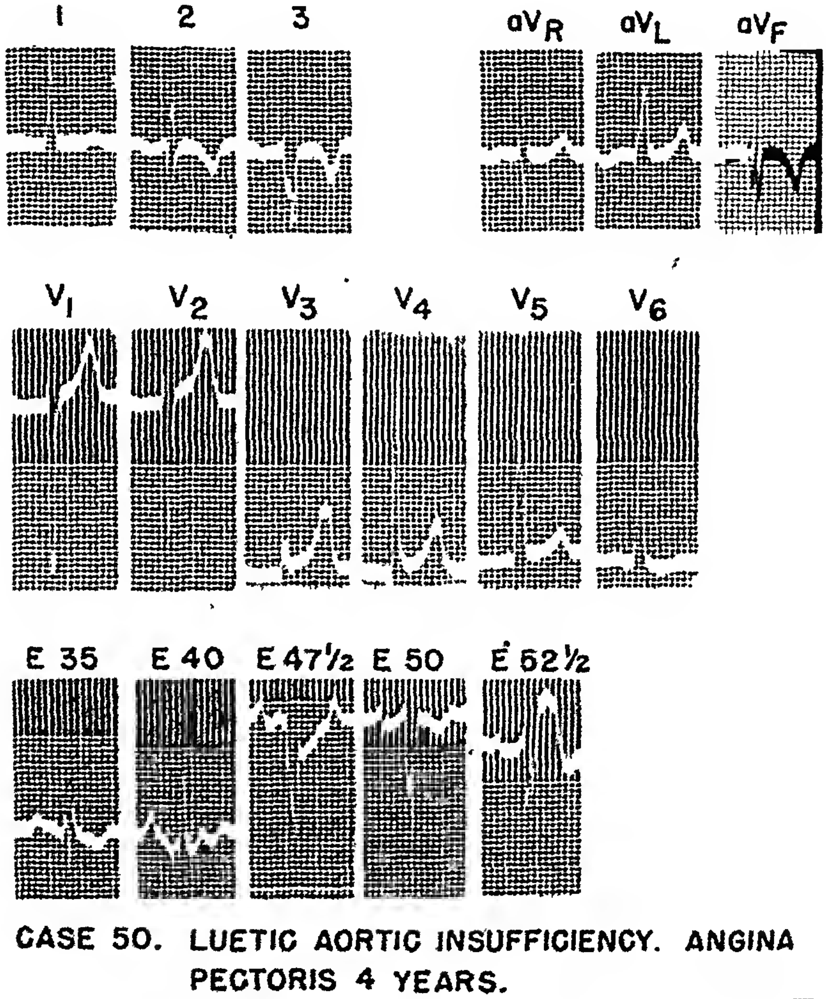


Fig. 9.—Coronary T waves in Leads II, III, aV_F, and Ev. Q waves absent.

2. Duration of QaV_F in the Two Groups: Of the twenty-two patients with infarction who showed QaV_F, this deflection was 0.04 second in duration or longer in only three instances (Cases 10, 16, and 48). In none of the uninfarcted controls did the QaV_F reach 0.04 second. Thus a QaV_F that is 0.04 second or more in duration is suggestive of posterior infarct, but is of rare occurrence.

3. Voltage of QaV_F in the Two Groups: In the twenty-two patients with infarct the voltage of QaV_F varied from 0.1 to 0.8 mv., while in the eight per-

*Complexes of this configuration are sometimes erroneously classed as Q waves. The presence of a definite antecedent R, even though small, indicates that the downward deflection is, by definition, an S, not a Q wave.

nosis of acute cor pulmonale was readily made electrocardiographically. Fig. 7 illustrates the appearance of a QS_3 type of complex both in patients with posterior infarction (Case 16) and in persons without infarction (Cases 17 and 18). Case 16 is readily differentiated from Cases 17 and 18 by the contour of the QRS in Lead aV_F but not by the contour of QRS_3.

C. *Comparison of Lead aV_F in Posterior Infarction With That in Uninfarcted Controls.*—

1. Incidence of QaV_F in the Two Groups: Since the potential of the posterior inferior surface of the left ventricle is transmitted through the diaphragm and intervening structures to the left leg, a Q wave in Lead aV_F would be expected if this aspect were infarcted. Of our twenty-four electrocardiograms of posterior infarction exhibiting a Q_3, a measurable Q wave occurred in Lead aV_F in all but two subjects (Cases 46 and 47, Fig. 8).

In both of these subjects, the acute attack had occurred approximately one year prior to this study and was established by typical serial changes in the electrocardiogram. Esophageal leads taken at the same time as Lead aV_F were typical of old posterior infarction. The presence of an abnormal Q wave in the esophageal leads and its absence in lead aV_F suggests that the infarct may have been located high on the posterior myocardial wall, near the auricular margin.

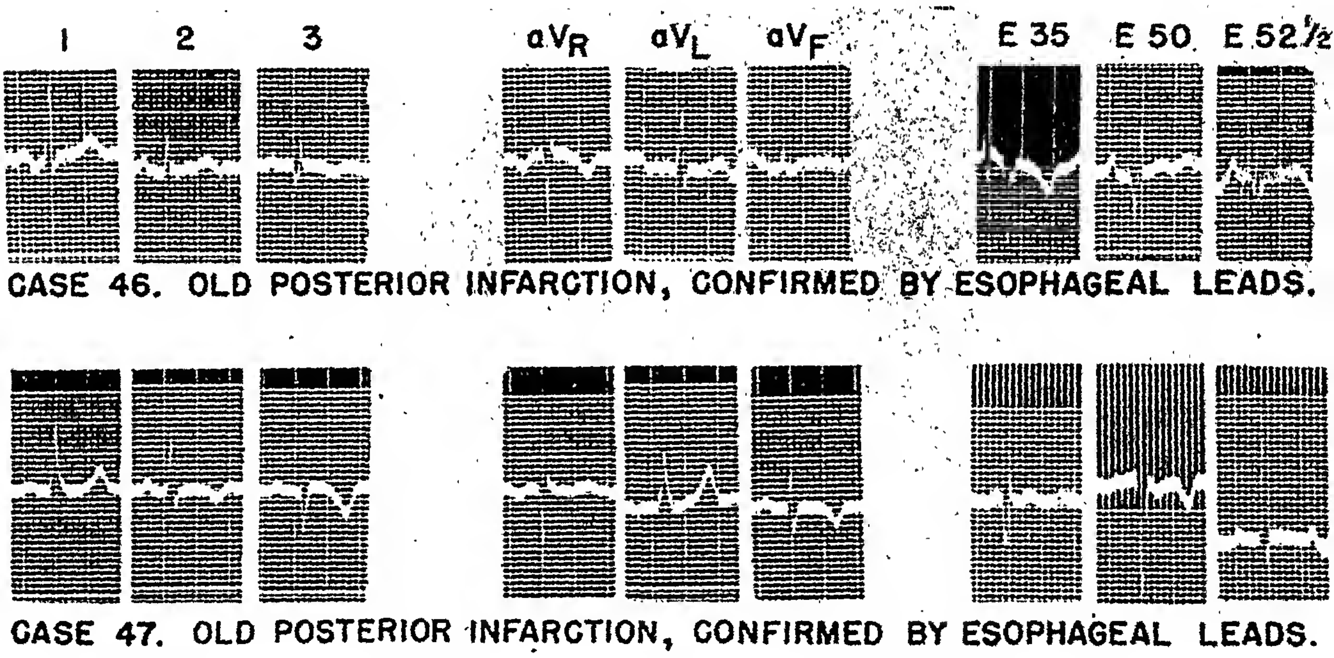


Fig. 8.—Cases in which Lead aV_F failed to reveal the presence of old posterior infarction.

This premise is supported by the fact that esophageal leads taken from a point 50 cm. from the nares were diagnostic of posterior infarction in Case 47, whereas leads taken at 52.5 cm. and below were normal. In Case 46 signs of posterior infarction were unmistakable at 50 cm. but had almost disappeared at 52.5 centimeters. Unfortunately no tracings were obtained at lower levels in this patient. If an infarct near the auriculoventricular junction does not extend a sufficient distance toward the apex to reach the diaphragmatic aspect of the left ventricle, one would anticipate no changes in aV_F even though the esophageal leads are diagnostic.

In Case 50 (Fig. 9), a small R and a deep S wave were found both in Lead aV_F and in standard Lead III instead of the classical QR or QS complex. The diagnosis of posterior infarction was made by the presence of cove-shaped T waves in Leads II, III, and aV_F, and was confirmed by esophageal leads. In all

A deep QaV_F followed by a small R wave, resembling the pattern in posterior infarction, was found in only one of the twenty-five subjects in whom posterior infarction had been excluded by history and esophageal leads (Case 45, Fig. 10). In this patient, there was clinical and electrocardiographic evidence of left ventricular hypertrophy. It is noteworthy that QaV_F was present only when the patient was in the recumbent posture, and disappeared completely when the patient was seated. Since Lead aV_F in the recumbent posture closely resembled V_1 and V_2, whereas Lead aV_L resembled Leads V_5 and V_6, it is evident that the heart was in the horizontal position, and the right ventricular potentials were transmitted to the diaphragm and left leg and the left ventricular potentials to the left arm. Thus the Q wave in Lead aV_F is analogous to that commonly observed in precordial leads over the right ventricle in patients with left ventricular hypertrophy. When the patient assumed the sitting posture, the lowering of the diaphragm probably caused sufficient rotation so that left ventricular potentials were directed, in part, toward the left leg, resulting in a small RSR complex. The reason for the deep Q_3 in the sitting, as well as in the recumbent, posture will be considered in the discussion.

Lead aV_F was misleading, then, in one of the persons without posterior infarction (Case 45, Fig. 10) and in two of the patients with infarction (Cases 46 and 47, Fig. 8). Although, on the whole, Lead aV_F proved more reliable than standard Leads II and III in the diagnosis of posterior infarction, these exceptions emphasize the fact the Lead aV_F is not infallible for this purpose. The information it supplies must be correlated with other electrocardiographic and clinical data to minimize error.

D. *Postural Variations of Q_3 and QaV_F.*—Standard and augmented unipolar extremity potentials were taken in the sitting and recumbent postures in eight persons in whom infarct was excluded and in one patient with posterior infarction. Q_3 was significantly deeper in the seated, than in the recumbent, posture in five of the eight uninfarcted controls, whereas the reverse was true in two subjects, and no difference was noted in one. A QaV_F was present in the recumbent, but absent in the seated, posture in one patient (Case 45, Fig. 10) whom we have already discussed. A very small QaV_F was present in the seated posture in one patient but absent in recumbency. The remaining six patients showed no Q wave in aV_F taken in either posture.

The subject with posterior infarction (Case 35) showed an abnormal Q wave in Leads III and aV_F in both postures, but significantly deeper in the recumbent, than in the seated, posture. It is thus evident that the presence of postural variations in the depth of Q_3 or QaV_F should not in itself be construed as evidence against the presence of an infarct.

COMMENT

1. *The Derivation of Lead III.*—The mechanism whereby the Q deflection is produced in Lead III is made clearer from an understanding of the derivation of that lead. The unipolar extremity leads are always taken with the exploring electrode connected to the positive terminal of the galvanometer and with an indifferent electrode of zero potential connected to the negative terminal. Thus a positive potential in the extremity connected with the exploring electrode is recorded as an upright deflection, a negative potential as a downward deflection. On the other hand, the standard leads are bipolar leads, each representing the fusion of the unipolar leads, which contribute equally but in opposite directions to the deflections of the galvanometer. Using Einthoven's equation, Lead III =

sons without posterior infarct it showed a similar range. It is thus evident that a normal and abnormal QaV_F cannot be positively distinguished by the absolute voltage.

When the voltage of QaV_F is considered in relation to that of the R wave in the same lead, a sharper differentiation may be made between the two groups.

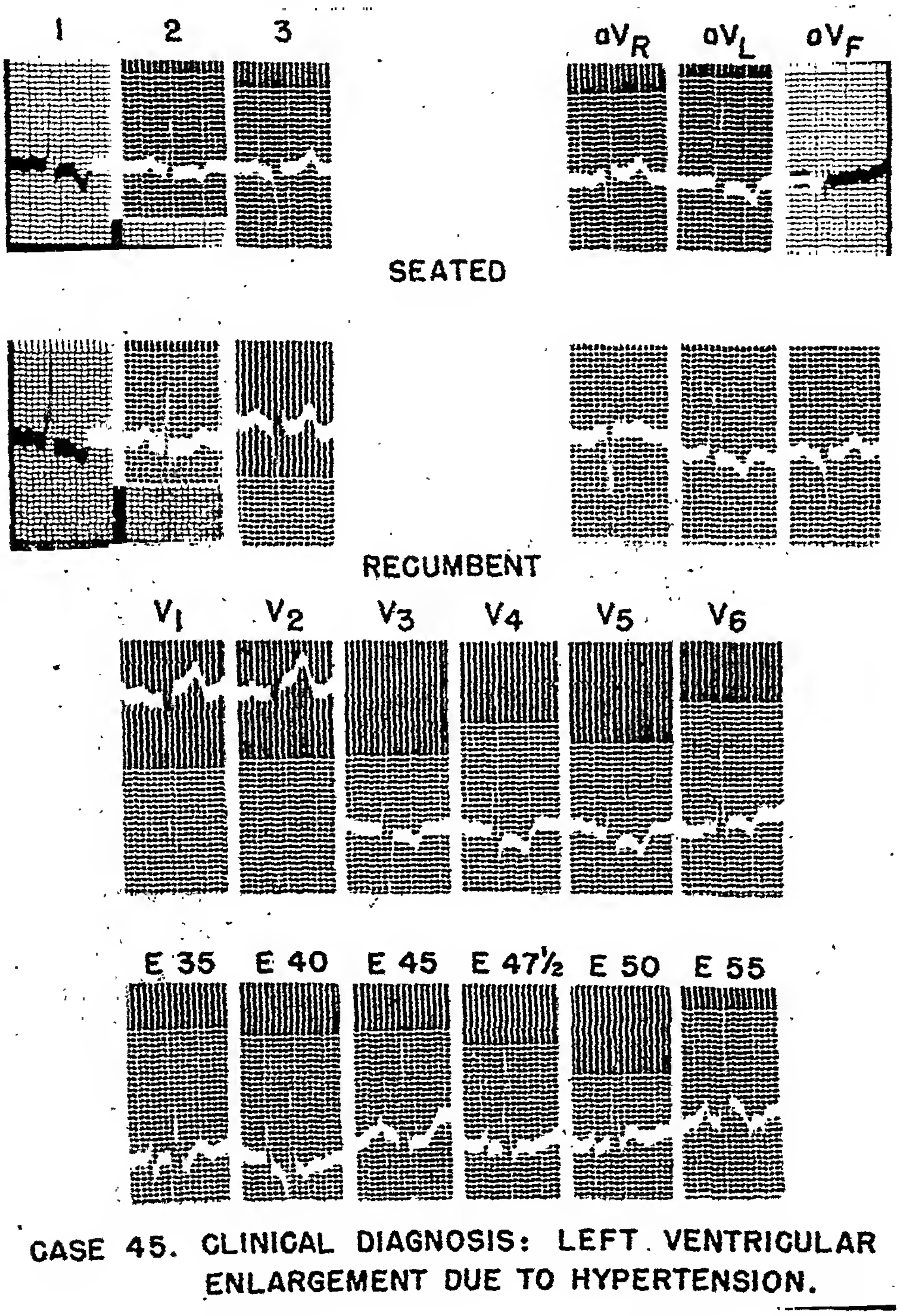


Fig. 10.—Marked postural variations in QRS in Lead aV_F. Misleading Q waves in this lead, taken in the recumbent position.

In the twenty-two tracings from patients with posterior infarction showing a Q deflection in Lead aV_F, the amplitude of the Q was more than 25 per cent of the succeeding R in every instance. On the other hand, a QaV_F which was more than 25 per cent of RaV_F was found in only three of the twenty-five persons without infarction (Cases 26, 29, and 45).

In two of these three persons (Cases 26 and 29), QaV_F was very small (measuring 0.13 and 0.2 mv., respectively) and was followed by R waves which were also of low voltage. It is doubtful if much significance can be attached to Lead aV_F when the voltage is so small.

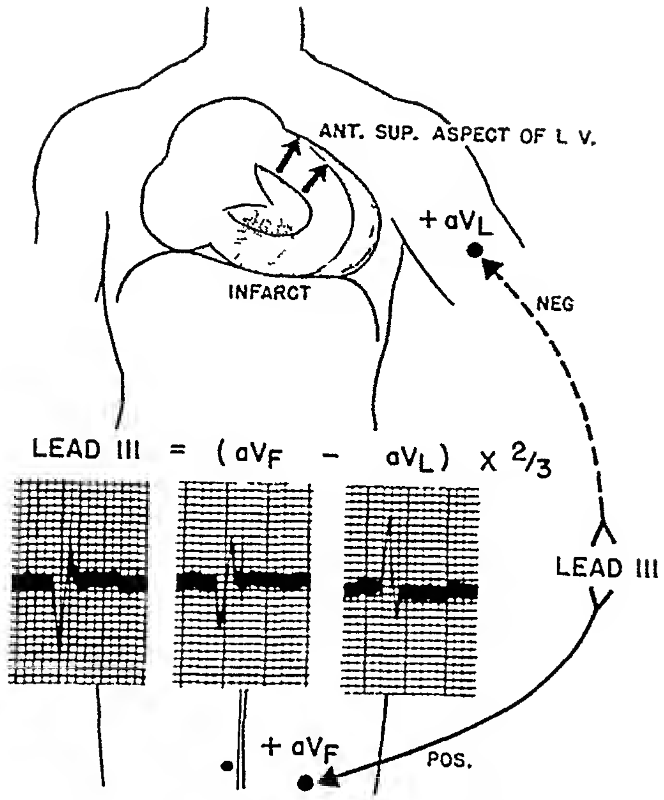


Fig. 11.—Abnormal Q waves in Leads III and aV_F due to infarction of the posterior diaphragmatic aspect of the left ventricle.

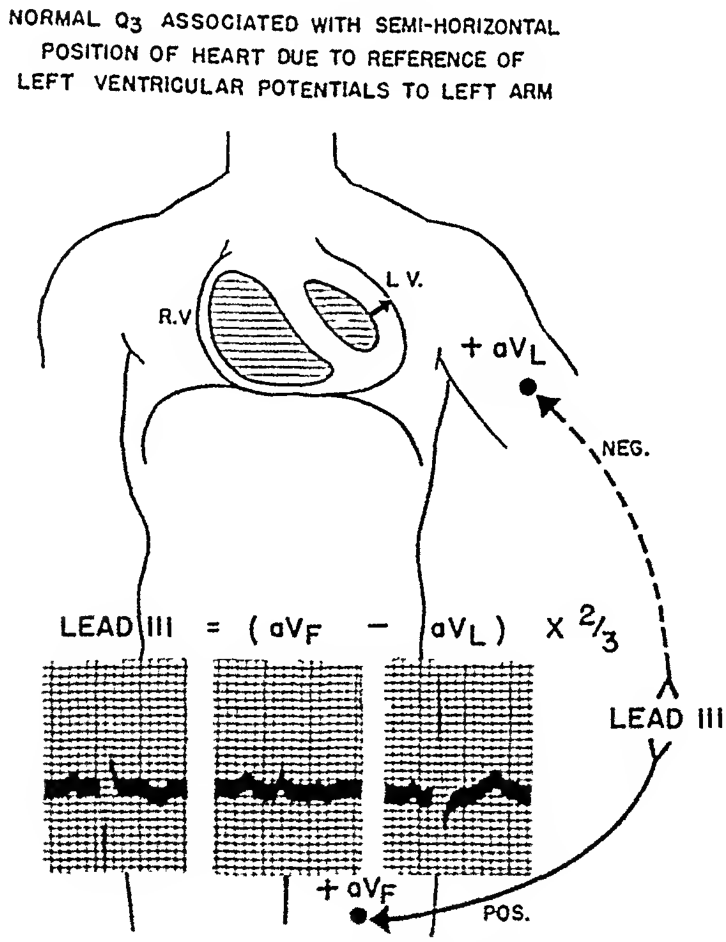


Fig. 12.—Normal Q_3 associated with semihorizontal position of the heart due to reference of left ventricular potentials to left arm.

Lead II – Lead I, Wilson, MacLeod, and Barker[39] demonstrated that Leads I, II, and III could be calculated mathematically from known unipolar extremity potentials from the right arm, left arm, and left leg (V_R, V_L, and V_F, respectively). By transposing these values into Einthoven's equation, they showed that Lead I must equal $V_L - V_R$; Lead II, $V_F - V_R$; and Lead III, $V_F - V_L$. Thus in taking Lead III, the left leg is connected to the galvanometer in the same manner as in taking the unipolar left leg lead, whereas the left arm is connected in the opposite manner, i.e., to the negative instead of to the positive pole. Hence, Lead III is derived either by subtracting V_L from V_F or by adding the mirror image of V_L to V_F.

Goldberger's[33, 34] augmented unipolar extremity potentials may be used in these same equations if the result is multiplied by two-thirds, since the deflections obtained when his indifferent electrode is used amount to one and one-half times the actual potentials in the extremities.

Thus:

$$\text{Lead I} = (aV_L - aV_R) \times 2/3,$$
$$\text{Lead II} = (aV_F - aV_R) \times 2/3,$$
$$\text{and Lead III} = (aV_F - aV_L) \times 2/3.$$

2. *The Derivation of Q_3 and QaV_F in Posterior Infarction.*—Wilson's[27] explanation of the origin of the Q wave in myocardial infarction is generally accepted and has been summarized in the introduction. Kossmann and de la Chapelle[43] have applied Wilson's concept to an explanation of the derivation of the Q wave in Leads II, III, and V_F in cases of posterior infarction. Fig. 11 represents this diagrammatically.

When an exploring electrode is applied to an extremity and an indifferent electrode of zero potential is used, the galvanometer of the electrocardiograph records potential variations in the extremity. The potential variations in the left leg are governed principally by those at the epicardial surface which customarily faces toward the left leg, namely, the epicardial surface of the postero-inferior (diaphragmatic) aspect of the left ventricle. While this portion of the ventricle is being activated in the normal heart by the passage of an impulse from the endocardial to the epicardial surface, the latter surface, as well as the left leg, is electro positive, resulting in the registration of an R wave in Lead aV_F.

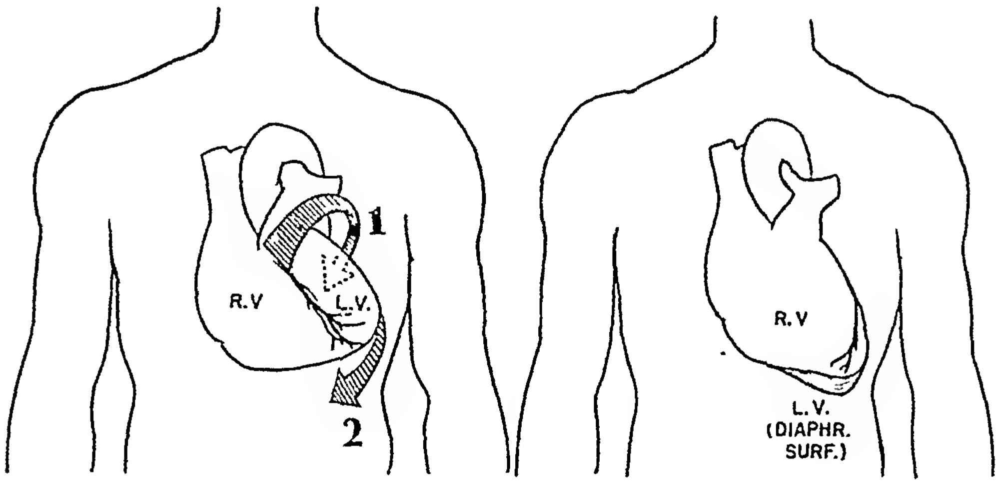
If the postero-inferior aspect of the left ventricle is completely infarcted, an impulse no longer passes through this portion of the ventricular wall. Thus, the epicardial surface reflects the potential variations of the cavity of the left ventricle. The ventricular cavity is electronegative while the impulse is passing from endocardium to epicardium in the uninfarcted portions of its walls. This electronegativity is reflected through the infarcted diaphragmatic wall to the left leg and is registered as a Q wave in Lead aV_F.

Since Lead aV_F is one of the two unipolar leads composing the bipolar standard Lead III, its Q wave contributes to the depth of Q_3. In addition, the unopposed, upwardly directed impulses in the uninjured anterosuperior wall (Fig. 11) of the left ventricle cause marked electropositivity at the epicardial surface directed toward the left arm, which is recorded in the unipolar lead from that extremity as a tall R wave. From the arithmetical derivation of Lead III, this contributes even more depth to the Q deflection in that lead.

3. *The Derivation of Q_3 in Semihorizontal or Horizontal Hearts.*—Just as the unipolar lead of the left leg reflects the potential at the epicardial surface of that portion of the heart which faces toward the left leg, the unipolar left arm

monary emphysema, or an elongated, asthenic chest wall, is more often associated with vertical position of the heart (Fig. 13, *b*).

Lewis[11] stated that a Q deflection was the first evidence of ventricular activation and represented the passage of an impulse through the ventricular



a. EXPIRATORY POSITION OF HEART ARROWS SHOW SUBSEQUENT ROTATION 1 UPON HEART'S OWN LONGITUDINAL AXIS AND 2 UPON ANTEROPOSTERIOR AXIS.

b. INSPIRATORY POSITION OF HEART AFTER COMPLETION OF ROTATIONS DESCRIBED IN a.

Fig. 13.—Changes in position of heart with respiration or posture.

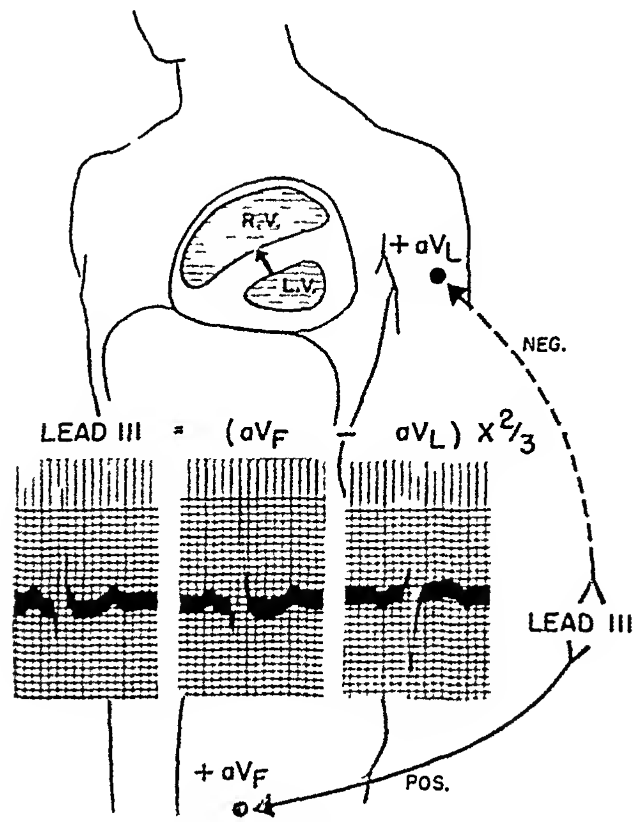


Fig. 14.—Normal Q_3 and QaV_F associated with vertical position of the heart due to activation of the left ventricular half of the septum.

septum. Mahaim[12] found that the first offshoots from the left bundle branch into the left half of the septum occurred at a point much nearer the bifurcation of the bundle of His than the first *offshoots from the right bundle branch into* the right half of the septum. From this he concluded that the anterobasal

lead (aV_L) is governed chiefly by the potential at the epicardial surface which faces toward the left arm (Wilson, et al.[37, 39]). When the heart is in the horizontal or semihorizontal position, the lateral and apical portions of the left ventricle face toward the left arm (Fig. 12); impulses passing from endocardium to epicardium in this portion of the wall during the activation of the ventricle result in electropositivity at the epicardial surface, which is represented as a tall R wave in Lead aV_L.

At the same time, the right ventricular surface of the horizontal or semihorizontal heart has been rotated to face more toward the left leg. Lead aV_F will resemble precordial Leads V_1 and V_2 if the right ventricular potentials are referred to the diaphragm (horizontal position), whereas it will be of very low voltage if a portion of the left as well as the right ventricle form the diaphragmatic surface of heart (semihorizontal position). Fig. 12 illustrates the production of a Q wave in the bipolar standard Lead III through the fusion of the unipolar leads from the left leg and left arm. Subtracting the tall left ventricular R wave of Lead aV_L from the small, upright or diphasic deflection of Lead aV_F will account for the deep downward deflection in standard Lead III, which, in some cases, may be an S wave, but in others may be a Q or QS wave as deep as any found in posterior infarction. This is a not an infrequent occurrence in persons with normal hearts which are semihorizontal in the electrical position. If left ventricular hypertrophy is present, Q_3 so produced may not only be deep, but also prolonged to 0.04 second or more.

As might be expected, the Q wave of horizontal or semihorizontal hearts is found only in Lead III, but not in Lead II, which is composed of the left leg and right arm potentials. The tall R wave of the left arm lead, which is the source of Q_3 in hearts which are in this position, is not represented at all in Lead II.

The six paired electrocardiograms in Figs. 3, 4, and 5 have already been mentioned. We return to these curves to re-emphasize the similarity of the standard leads in each pair. However, by reference to Lead aV_F, a clear-cut differentiation may be made between patients with posterior infarction and normal subjects.

4. *The Derivation of Q_3 in Vertical Hearts.*—In studying the effect on the electrocardiogram of positional changes in the dog's heart, Meek and Wilson[40] found that when the apex was moved to the right on an axis extending anteroposteriorly through the body, curves characteristic of right axis deviation were obtained. Similar curves were produced with rotation of the heart on *its own* longitudinal axis, so that the front of the heart was turned more to face the left. These two types of rotation are represented diagrammatically in Fig. 13. Experimentally, in the dog, the rotation could be limited to one or the other of two axes, but combined rotation on both axes was found to occur when the heart was displaced to one side.

An interesting study of rotation of the human heart was done by Kountz, Prinzmetal, Pearson, and Koenig.[41] By perfusion of the heart immediately after death, they were able to reactivate it and to obtain reasonably normal electrocardiograms. Curves typical of right axis deviation were obtained when the heart was rotated clockwise on its own axis (Fig. 13, arrow *1*), whereas the reverse was true upon counterclockwise rotation. Elevation of the diaphragm, whether due to deep expiration, recumbent posture, or obesity, may be associated with a horizontal or semihorizontal heart (Fig. 13, *a*). On the other hand, the lower position of the diaphragm due to deep inspiration, erect posture, pul-

QaV_F, esophageal leads suggested that the infarct was located high on the posterior wall, near the auricular margin. The voltage of the QRS wave in Lead aV_F was low in two of the three uninfarcted controls which showed a Q/R ratio exceeding 25 per cent in this lead. In the remaining case, the deep Q wave was present in Lead aV_F when the patient was recumbent, but disappeared when the curve was taken with the patient in the erect posture.

The mechanism of production of the Q wave in standard Lead III has been discussed separately for (a) that associated with posterior myocardial infarction, (b) that occurring in uninfarcted hearts with a horizontal or semihorizontal electrical axis, and (c) that occurring in uninfarcted hearts with a vertical electrical axis.

CONCLUSIONS

1. The contour of the QRS complex in the augmented unipolar left leg lead (Lead aV_F) is of considerable value in the differentiation of the normal from the abnormal Q wave in standard Lead III.

2. The presence of a Q wave in Lead aV_F which is more than 25 per cent of the voltage of the R wave in the same lead constitutes strong but not absolutely pathognomonic evidence for the existence of a posterior myocardial infarct.

3. The absence of a QaV_F or the presence of an insignificant deflection which is less than 25 per cent of the subsequent R wave constitutes strong but not absolutely conclusive evidence against the presence of a posterior myocardial infarct.

We wish to express our appreciation of the work of Miss Evelyn Erickson, Miss Geraldine Chesney, and Mr. Clayton Oliver in preparing the illustrations.

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aspect of the left side of the interventricular septum was the first portion of the ventricle to be activated, and it gave rise to the very beginning of the QRS deflection.

Septal activation not only is initiated on the left side, but also preponderates on that side due to the fact that the left ventricular portion of the septum is thicker than the right. Thus, the resultant electrical vector can be represented by an arrow (Fig. 14) passing from the left ventricular cavity toward the right.

In the vertical position (Fig. 13, *b*) combined rotation of the heart upon an anteroposterior axis extending through the body (Fig. 13, *a*; arrow *1*) and upon its own longitudinal axis (Fig. 13, *a*; arrow *2*) causes the right ventricle to lie anterosuperiorly and the left, postero-inferiorly. Fig. 14 is a diagram of an oblique section through such a vertical heart, to show the relation of the septum to the ventricular cavities. The arrow in Fig. 14 represents the vector associated with activation of the septum. Since the right ventricle lies above and in front of the left in the vertical heart, this arrow must be directed upward, giving rise to a Q wave in Lead aV_F which is carried over into standard Leads II and III.

The septal Q wave is of very brief duration, since the electrical changes in the rest of the myocardial wall rapidly take ascendency. This septal Q wave is followed by a relatively tall R wave due to activation of that portion of the left ventricle which lies opposite the septum. When the heart is vertically placed, the major portion of the left ventricle is directed toward the diaphragm, giving rise to the tall R in Leads aV_F, II, and III, which follows the relatively small septal Q wave. The Q/R ratio is well below the limit of 25 per cent.

SUMMARY

An attempt was made to evaluate the diagnostic significance of the QRS pattern in the augmented, unipolar left leg lead (Lead aV_F) as a means of establishing or excluding the diagnosis of posterior infarction. Forty-nine patients were selected for study because of the presence of a prominent Q wave in standard Lead III. One additional patient with posterior infarction was included. This patient did not have Q waves but exhibited the classical ST-T wave changes in Lead III.

Multiple precordial and unipolar extremity leads were taken on every subject and esophageal leads were taken on forty-four of the fifty subjects. The presence of a posterior infarct was established in a total of twenty-five subjects, in four of these by autopsy, and in the remaining twenty-one by typical esophageal leads. The infarct was months or years old in all but four cases. Posterior infarction was excluded in a total of twenty-five subjects, in three by autopsy and in the remaining twenty-two by negative esophageal leads.

In all cases where posterior infarction was excluded, a prominent Q_3 or QS_3 was present. This amounted to 25 per cent or more of the tallest R in twenty-three of the twenty-five cases; from an examination of the standard leads alone, many of these cases could not be distinguished from cases proved to have old posterior infarction. The pattern of the QRS in Lead aV_F proved to be of considerable help in this differentiation.

A QaV_F which was 25 per cent or more of RaV_F was found in twenty-two of the twenty-five subjects proved to have posterior infarct, and in only three of the twenty-five subjects in whom the diagnosis of posterior infarction had been excluded. In both cases of posterior infarct which had a Q_3 but failed to show

DELAYED CONDUCTION IN THE BUNDLE BRANCHES

A Report of Two Cases in Which the P-R Interval Increased With Changes From Left to Right Bundle Branch Block

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THE occurrence of incomplete or partial* bundle branch block has been postulated on theoretical grounds[1] in analogy to the disturbances of conduction which result from lesions of the main stem of the bundle of His. In animal experiments various kinds of partial block in the bundle branches have been produced.[1-4] The clinical diagnosis of incomplete bundle branch block, however, meets with considerable difficulties. This is in part due to the fact that the transmission of impulses in the bundle branches is included in the auriculoventricular conduction time. Therefore, a disturbance of conduction which involves equally both bundle branches produces electrocardiographic changes indistinguishable from those caused by lesions of the main stem of the bundle. Interruption of conduction in both bundle branches brings on complete auriculoventricular dissociation. Or, if there is an equal delay of conduction in both bundle branches, it is added to the auriculoventricular conduction time causing prolongation of the P-R interval. If, on the other hand, the delay of conduction is unequal in the two branches or affects one bundle branch only, asynchronous activation of the ventricles results, causing widening of QRS. In those cases where the delay of conduction in one bundle branch is longer than the time required for the excitation transmitted through the other branch to reach the affected ventricle by way of the interventricular septum, the resulting widening and deformation of QRS is the same as that caused by complete bundle branch block.[3] In the dog, for instance, a delay of conduction in one bundle branch measuring 0.04 second or more cannot be differentiated in the electrocardiogram from complete interruption of conduction produced by cutting the bundle branch. If the delay of conduction is less than 0.04 second aberrations of the ventricular complexes of variable degree are observed similar to those which result from combining the levocardiogram and the dextrocardiogram in variable time relations.[3]

It is, therefore, understandable that the clinical diagnosis of incomplete bundle branch block is based more often on conjecture than on unquestionable evidence. It has been suggested that bundle branch block which is but temporary is due to delay rather than interruption of conduction.[1] Also, the occurrence, both in the experimental animal[1-4] and clinically,[5,6] of gradual transition of aberrant ventricular complexes which are characteristic of bundle branch block into normal complexes, has been explained by gradual increase in the conductive capacity of a bundle branch in the presence of incomplete bundle branch block. Precordial leads occasionally reveal right bundle branch block, although the duration of QRS is not more than 0.1 second. Such disturbance has been interpreted as due to incomplete bundle

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Received for publication Oct. 7, 1944.

*The terms "incomplete" and "partial" bundle branch block are used here synonymously to denote either delayed or intermittent conduction in the bundle branches as opposed to complete interruption of conduction.

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in the right bundle division. Right and left bundle branch complexes alternated in the same tracing (Fig. 2) without showing any constant relation to the variable length of the sinus period. The most striking feature was a prolongation of the P-R interval which accompanied every change from left to right bundle branch block. Those complexes presenting the features of left bundle branch block had a P-R interval of 0.18 second, whereas the beats with the characteristics of right bundle branch block showed a P-R interval measuring, on the average, 0.23 second.

Fig. 2.—Case 1. The same two types of ventricular complexes are noted as in Fig. 1, but they alternate in irregular intervals. Most of the beats belong to the type which is characterized by upward QRS in Lead I, suggestive of left bundle branch block. Their P-R interval is 0.18 second. The second type is seen in Leads II and III only; it is characterized by deep Q waves and high R waves, suggestive of right bundle branch block. The P-R interval of these beats is 0.23 second. (Time intervals equal 0.05 second.)

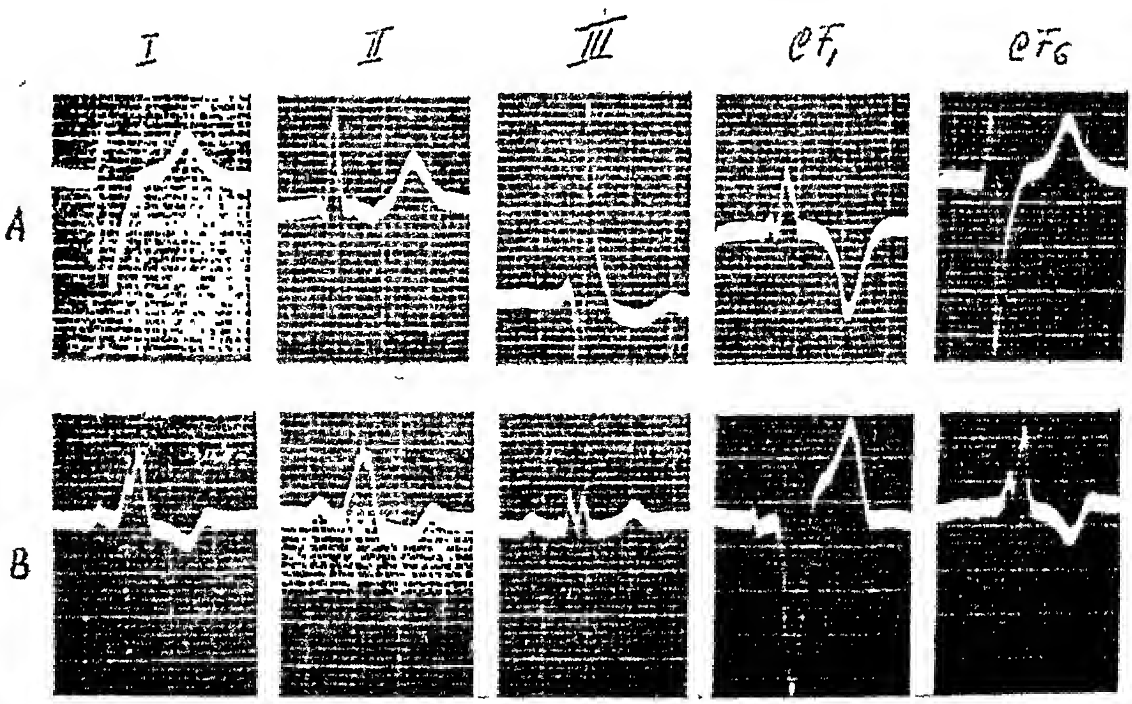

Fig. 3.—Case 2. Two types of ventricular complexes are noted. In both the duration of QRS is 0.16 second. One type (A) shows a prominent broad S wave in Lead I, suggestive of right bundle branch block. In Lead CF_1, the QRS complex is upright and bifid; in Lead CF_6 a prominent broad S wave is noted.

Tracing B presents the other type of ventricular beats which is characterized by upright QRS complexes in the limb leads. In Lead CF_1 there is a broad QS wave; in Lead CF_6 the QRS complex is upright, broad, and notched. These are the features of left bundle branch block.

Case 2.—M. Y., a white man, aged 51 years, had always been well and had never complained of his heart. Four weeks prior to admission to the hospital he suffered syncope which lasted for a few minutes. A similar attack occurred a week later. A day prior to

branch block.[7] Furthermore, cases are on record in which normal ventricular complexes alternate regularly with grossly aberrant forms suggesting the presence of partial bundle branch block with a conduction ratio of 2:1, 3:1, or 4:1.[5, 8-11] These observations present the most obvious instances of partial block in the bundle branches. Far more difficult, for reasons which have been discussed, is the diagnosis of a simple delay of intraventricular conduction in one bundle branch. Such disturbances may be disguised as complete bundle branch block,[3] if the other bundle branch has preserved its conductive capacity; or as prolonged auriculoventricular conduction time, if the second bundle branch fails to conduct properly. In the experimental animal it is possible by cutting one bundle branch and injuring the other to produce, in addition to aberrant ventricular complexes characteristic of block of the severed bundle branch, either prolongation of the P-R interval or dropped ventricular beats. Conditions as favorable for the analysis of intraventricular conduction disturbances are rarely met in clinical instances. We have observed two cases in which alternation of right and left bundle branch block provides what seems to be stringent evidence of delayed conduction in a bundle branch. These cases are the object of this report.

Fig 1.—Case 1. Two types of ventricular complexes are noted; in both the duration of QRS is 0.12 to 0.13 second. One type (*A*) shows an upward directed main deflection in Lead I, suggestive of left bundle branch block. Its P-R interval is 0.17 second. The other type (*B*) presents a downward directed main deflection in Lead I, indicative of right bundle branch block. Its P-R interval is 0.23 second. (Time intervals equal 0.05 second.)

CASE REPORTS

Case 1.—K. W., a white woman, aged 76 years, had suffered an attack of protracted severe pain across the chest six weeks prior to examination. The pain was associated with cold sweat. Since then, when walking, the patient had experienced pressure in the chest which forced her to stop for a while. Physical examination revealed a blood pressure of 130/60 mm. of mercury. A broad, heaving apical thrust was noted; this pointed, in the absence of significant murmurs, to previous hypertension. Fluoroscopy showed distinct enlargement of the heart to the left and deposits of lime salt in the aorta.

The electrocardiogram (Fig. 1) revealed sinus arrhythmia with an average rate of 88 per minute. Two types of ventricular beats were noted; both had deformed complexes, and the duration of QRS measured about 0.13 second. One type showed upright initial deflections in Lead I (Fig. 1, *A*) suggesting the presence of left bundle branch block. The other type presented a downward directed QRS in Lead I (Fig. 1, *B*) pointing to a lesion

delay the stimulus transmitted by the right bundle branch is able to reach the left ventricle and to activate both chambers. The resulting ventricular complexes show the features characteristic of complete left bundle branch block. At times, however, when the right bundle branch fails to transmit the excitation in due time (because of either interruption or marked delay of its conduction), the left division of the bundle activates not only the left but also the right ventricle. Its conduction delay is then added to the A-V conduction time, and the ventricular complexes which present the features of right bundle branch block have a P-R interval which is prolonged by 0.05 second.

It is conceivable that the occasional occurrence of dropped ventricular beats in Case 2 was due to further impairment of the conduction in the bundle branches. Similar conduction disturbances have been produced in the experimental animal by cutting one bundle branch and exerting pressure on the other branch.[3, 4] However, the available evidence in our case does not allow us to decide whether the periods of ventricular standstill were caused by the lesions in the bundle branches or by a concomitant obstruction in the path of the main stem of the bundle of His.

The occurrence of bilateral bundle branch block has been occasionally recorded in clinical instances.[12, 13] In fact, it might be expected even more frequently than is suggested by the few cases on record, for anatomic studies have shown that what is usually diagnosed as unilateral bundle branch block is commonly associated with bilateral lesions.[14] One of the cases reported in the literature[12] bore striking resemblance to our Case 2 but was given a different interpretation.

SUMMARY

Two cases are reported which, in the electrocardiogram, presented aberrations of the ventricular complexes of two types, suggestive of alternation of right and left bundle branch block. Changes from left to right bundle branch block were invariably accompanied by prolongation of the P-R interval; the increase measured 0.05 second or more. This fact suggested that what first appeared to be complete left bundle branch block was actually a delay of conduction in the left division of the bundle measuring 0.05 second. The delay in the left branch allowed the excitation, passed by the right bundle branch, to reach the left ventricle and to activate both chambers. At times, however, when the conduction in the right bundle branch failed, the left branch of the bundle took over the task of activating not only the left but also the right chamber. The delay of its conduction was then added to the A-V conduction time, causing a prolongation of the P-R interval by 0.05 second.

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admission the patient experienced a number of dizzy spells. On the day of admission he had several attacks of syncope with convulsions. Physical examination revealed distant heart sounds and bradycardia with arrhythmia; the cardiac rate varied from 38 to 60 beats per minute.

Various electrocardiograms were taken which revealed the presence of partial A-V block with dropped beats. Two types of ventricular complexes were observed (Fig. 3). One (*A*) presented the features of right bundle branch block; the other (*B*) showed the characteristics of left bundle branch block.

In an electrocardiogram that was taken on March 31, 1944, both types of ventricular beats were present (Fig. 4). The tracing showed a regular sinus rhythm with a rate of 75 per minute. The P waves, with few exceptions, were followed by ventricular beats which, apparently, were conducted from the auricles. The beats which were suggestive of left bundle branch block presented upright QRS deflections in all leads. The other type, suggestive of right bundle branch block, showed prominent broad S waves in Lead I and deep Q waves and high R waves in Leads II and III. The two types of ventricular complexes alternated in varying intervals, and the changes from left to right bundle branch block were invariably accompanied by a prolongation of the P-R interval. Those beats indicative of left bundle branch block had a P-R interval of 0.16 second, while the other complexes which displayed the features of right bundle branch block were preceded by P waves in an interval of 0.21 second. The latter complexes were occasionally followed by auricular waves which were not conducted to the ventricle (Fig. 4, Lead I).

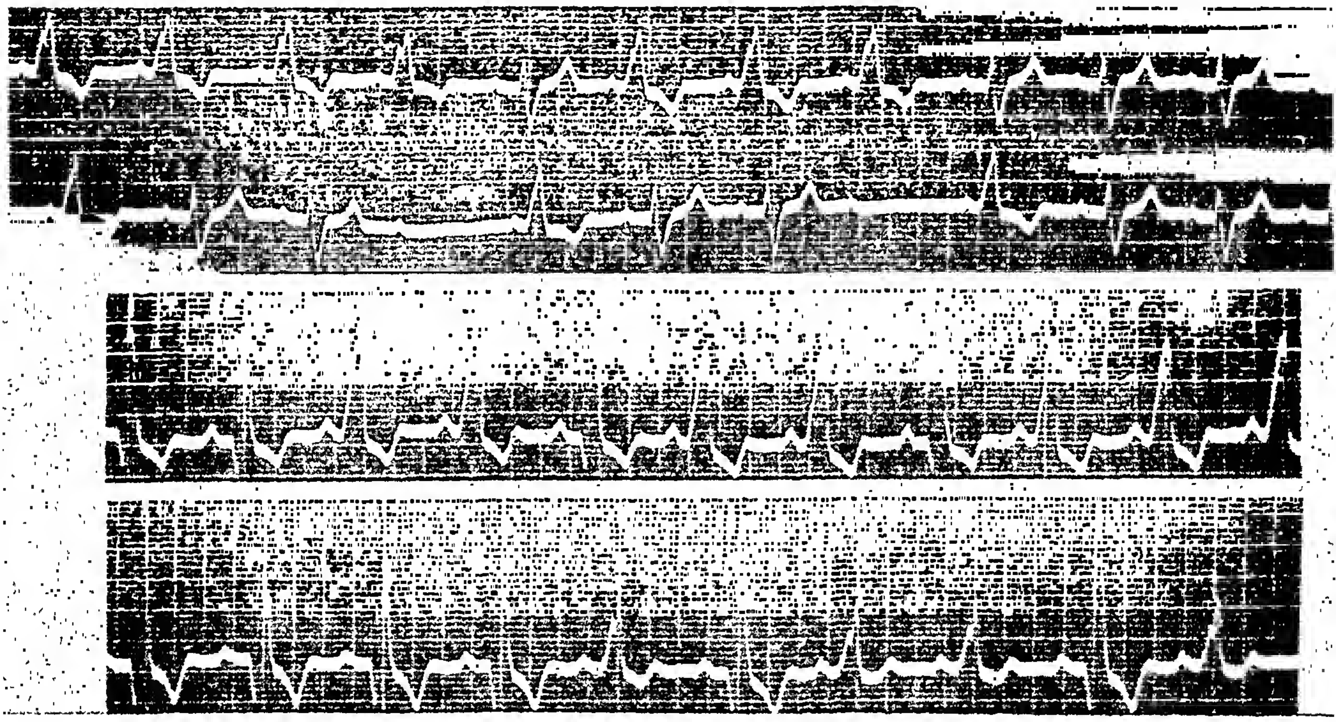

Fig. 4.—Case 2. There is a fairly regular sinus rhythm with two types of ventricular complexes similar to those seen in Fig. 3. In both the duration of QRS is 0.16 second. One type is characterized by an upward directed QRS in all leads suggestive of left bundle branch block. Its P-R interval is 0.16 second. Another type of beats presents deep wide S waves in Lead I, and marked Q waves and high R waves in Leads II and III. These beats seem to indicate right bundle branch block. Their P-R interval is 0.21 second. Most of the auricular waves are followed by ventricular complexes. Only in Lead I some of the ventricular complexes which present deep S deflections are followed by blocked P waves. (Two strips of a continuous tracing are shown in Lead I.)

COMMENT

The two cases reported here present in the electrocardiogram changes which suggest lesions in both bundle branches. Left and right bundle branch block complexes alternate in irregular sequence, but changes from left to right bundle branch block are invariably accompanied by prolongation of the P-R interval; the increase was at least 0.05 second. This feature affords a clue for the analysis of the conduction disturbance in the left bundle branch. It suggests that the left division of the bundle requires 0.05 second more than the right bundle branch to pass the stimulus to the ventricle. Because of this

unipolar limb leads,[5] as obtained on patients with various forms of cardiac disease and on control subjects. On every individual selected for that study, electrocardiograms are secured which include Leads I, II, III, and IVF, the CF, CL, CR, and V types of leads from precordial positions 1 to 6, inclusive, and the V type of unipolar limb leads. For recording these electrocardiograms, a standard electrocardiograph,* supplemented by a "Wilson central terminal,"[6,8] was initially employed. However, to secure the required series of leads with such equipment, it is necessary to effect in every case numerous interchanges in the lead-wires attached to the electrodes on the patient. These manipulations of the wiring arrangements proved tedious and complicated, and recording the required electrocardiograms with such equipment was an inconvenient and time-consuming procedure. Therefore, the switching device herein described was developed in order to simplify and facilitate the recording technique for the previously mentioned study.

This switch, when employed either for investigative or for ordinary clinical purposes, has been found extremely convenient for the recording of electrocardiograms embodying multiple types of leads. Since it is believed that the practical advantages of this simple device should be made more widely available, publication of directions for its construction and use seems warranted.

MATERIALS FOR CONSTRUCTION

The materials needed for the construction of this switching device can be obtained without particular difficulty, even in these days of priorities, at regular stores dealing in standard electrical and radio parts and supplies. The total cost of the completed switch, when no labor charges for assembling are included, is approximately $10. The individual items required for the construction are:

A. Four "radio-type" rotary switch sections, each providing eight distributed switch positions and one common contact pole.†

B. One switch kit, for assembling the individual switch sections into the switch-supporting chassis.†

C. One switch bar-knob.

D. One 12-foot length of "four-way," rubber-insulated, shielded microphone cable, containing four rubber-insulated, 26-strand wires.

E. Four 4-foot lengths of pliable, rubber-insulated, 26-strand wire for constructing the lead-wires going to the electrodes on the patient.

F. One 4-way coupling connection, for insertion between the 4-wire microphone cable and the four lead-wires. This may be improvised on any suitable basis.

G. Four "radio-type" terminal plugs (or alligator clips, if preferred) for attaching the individual lead-wires to the electrodes on the patient. These must be suitably marked for ready identification; as illustrated, one stripe, two stripes, three stripes, and four stripes identify, respectively, the terminal plug used for attaching the proper lead-wire to the right-arm, the left-arm, the left-leg, and the precordial (exploring) electrode.

H. Three 5,000-ohm, 1-watt resistors.

I. Three terminal binding posts (banana jacks) for attachment to the outside of the switch box.

J. One switch housing, for mounting and enclosing the composite switch. (A standard wooden filing box, as used for 3 by 5 inch index cards will serve satisfactorily for this purpose.)

K. Twelve marking tacks, ¼ inch in diameter, with celluloid-covered, flattened heads. These are used to identify the three terminal binding posts located on the outside of the switch box and the contact points about the switch bar-knob constituting the individual stations of the lead-selector, and can be properly marked for that purpose with India ink.

L. One 20-foot length of rubber-insulated, 26-strand wire, fitted with suitable contact points or clips, for use in grounding the switching device to an outside ground connection.

*As manufactured by the Cambridge Instrument Company, Inc.

†For this purpose we have used Type U, 1 Pole 11 Position Steatite switch sections, and the switchkit Index Assembly "K123," both manufactured by Centralab, Milwaukee, Wisconsin.

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A SIMPLE SWITCHING DEVICE TO FACILITATE THE RECORDING OF ELECTROCARDIOGRAMS EMBODYING MULTIPLE TYPES OF LEADS

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Since 1932,[1, 2] precordial types of leads have been widely used and accepted in electrocardiography as of definite value to complement the three limb leads of Einthoven for practical clinical purposes. During this interval, however, a considerable diversity of opinion has developed concerning the "best" location for the distant electrode and the number of chest positions that must be explored[3-5] in order to derive from precordial leads, as conveniently as possible under ordinary clinical circumstances, the most reliable and truly practical information they afford. Additional leads of special types[6-8] have also been introduced to complement or to substitute for the three limb leads for clinical purposes, but these special leads have not yet been extensively explored as regards their practical merits or reliability. It happens, therefore, that various combinations of the three limb leads with different types and numbers of precordial leads, and sometimes with other special leads, are now being employed routinely or otherwise in clinical electrocardiography, and that controversy and uncertainty exist regarding the relative virtues of these various combinations. Because of these developments, it now seems evident that many additional experimental and clinical studies will need to be contributed on the problem of electrocardiograms embodying multiple types of leads, before any satisfactory standardization of their techniques and interpretations for practical clinical use can be finally accomplished. Moreover, in consideration of the more practical aspects of this problem, it seems important that attention be given to the development of simplified methods whereby electrocardiograms embodying multiple types of leads can be recorded with convenience under ordinary clinical circumstances.

In a study now being conducted, one of us[9] is attempting to find the direct comparative evaluation of electrocardiographic records which combine the three limb leads with different types and numbers of precordial leads,[3-5] and with

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The expenses of this study were borne in part by contributions from the Cardiac Research Fund of the George Washington University School of Medicine, and in part by a grant from the Lederle Laboratories, Inc.

Received for publication Oct. 11, 1944.

*Since making his contribution to this paper, Dr. Ethridge has entered on active duty with the U. S. Navy.

on each switch section is identified as Point *X*. From the clearly marked terminal plugs, which serve for attaching the lead-wires to the electrodes on the patient, the four lead-wires pass by way of the four-wire microphone cable into the switch box, and are distributed as follows: The wire from the right-arm terminal plug goes to Points *1* and *2* on Switch *B*, thence to Point *6* on Switch

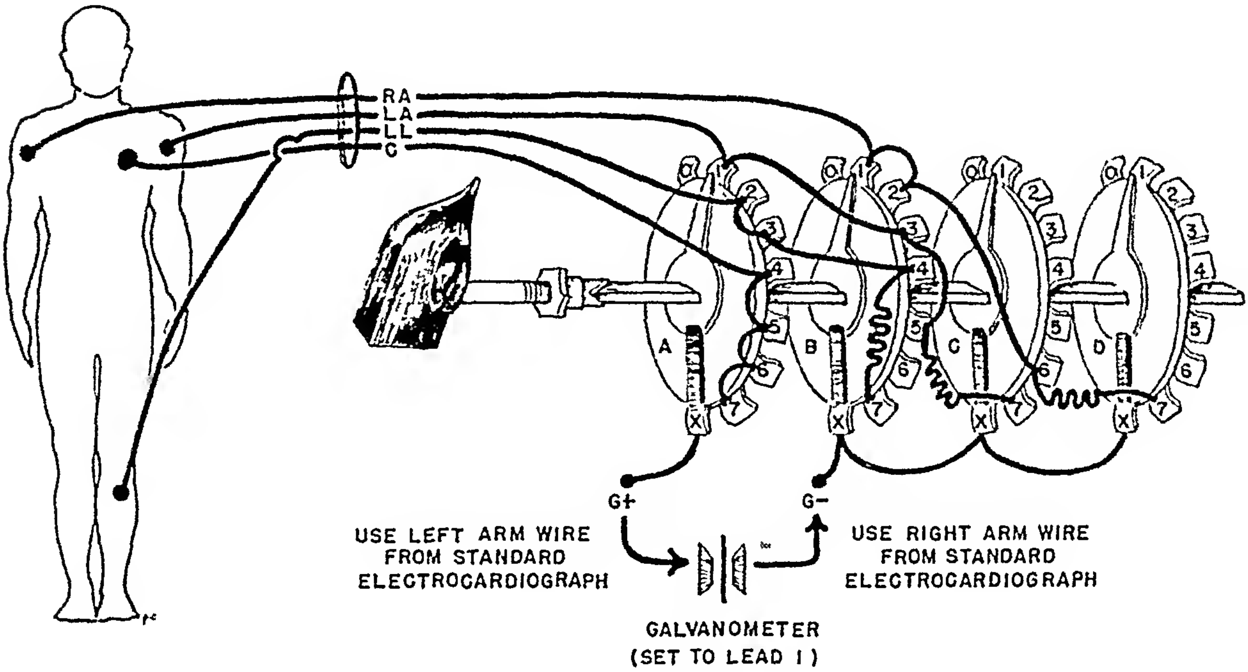

FIGURE 2. DIAGRAMMATIC DETAIL OF SWITCH CONSTRUCTION

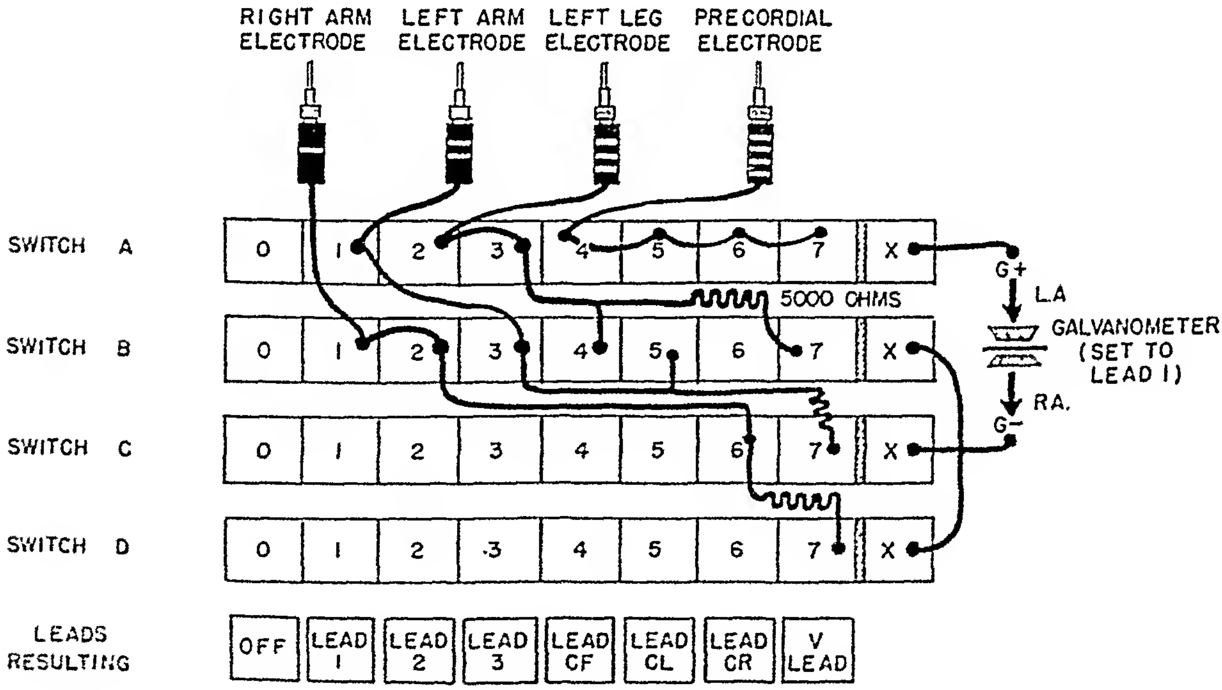

FIGURE 3. WIRING DIAGRAM

C, and finally through a resistor of 5,000 ohms to Point *7* on Switch *D*; the wire from the left-arm terminal plug goes to Point *1* on Switch *A*, thence to Points *3* and *5* on Switch *B*, and finally through a resistor of 5,000 ohms to Point *7* on

M. Four metal angle brackets, 1 by ½ by 1/16 inch, or other suitable means for fastening the switch box to the frame of the electrocardiograph or to the supporting table.

DETAILS OF CONSTRUCTION AND USE

The composite switch, mounted in a wooden box to protect the switch assembly and wiring, is shown in Fig. 1. This figure illustrates in perspective the clearly marked terminal plugs for attaching the lead-wires to the electrodes on the patient, the coupling connection used to convert the four lead-wires into the lead cable, the three terminal binding posts on the outside of the switch box (*G+*, *G–*, and *GND*), and the lead-selector consisting of the switch bar-knob and labelled stations. The switch bar-knob is located on the top face of the switch box and is encircled by markers located at the individual points of switch contact. These markers are clearly labelled *OFF, 1, 2, 3, CF, CL, CR,* and *V,* respectively, in a clockwise manner and in this sequence, to form the individual stations of the lead-selector.

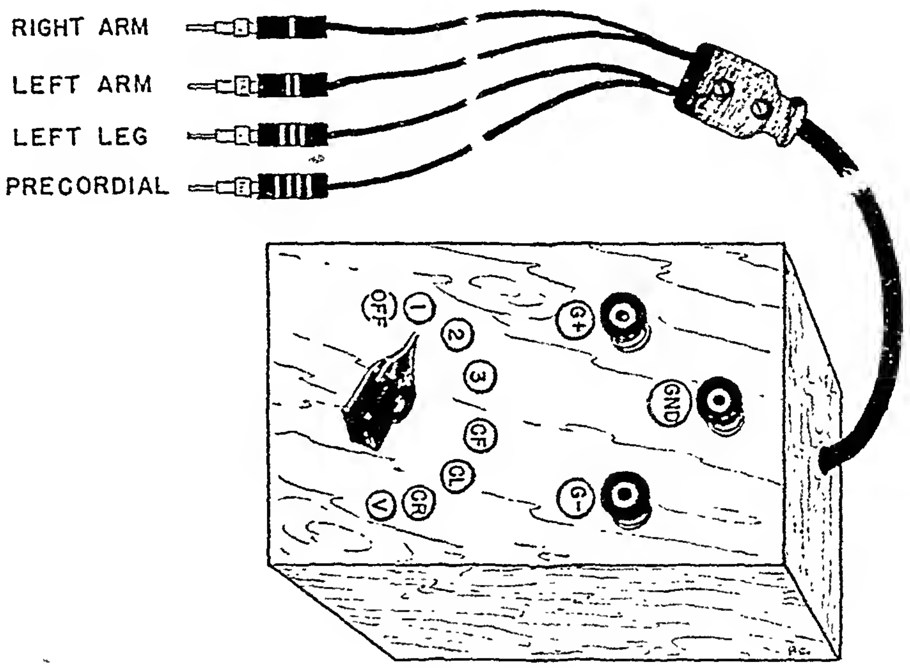

FIGURE I. THE COMPOSITE SWITCH

Fig. 2 is a diagrammatic representation of the assembled switch. The four switch sections are mounted in tandem on the same axis and are embodied in the switch assembly framework (latter not shown). The switch bar-knob is indicated mounted on the switch axis. The individual switch sections and the switch bar-knob are shown as widely separated in Fig. 2 in order that points of identification may be more clearly illustrated, but, in the actual construction, these units are mounted quite close together (not more than ½ inch apart), thereby reducing the overall size of the assembled switch. Also incorporated in this figure is a schematic representation of the wiring arrangements necessary to secure the proper circuit connections for Leads I, II, and III, and the CF, CL, CR, and V types of leads, respectively, with the use of this switch.

A complete wiring diagram for the switch herein described is shown in Fig. 3. In the text and in Figs. 2 and 3, in order to clarify the wiring description, the four individual switch sections are identified as Switches *A, B, C,* and *D,* respectively; the eight distributed points on each of the switch sections are identified, in a clockwise manner as seen from the top of the composite switch, as Points *0, 1, 2, 3, 4, 5, 6,* and *7,* respectively; and the common contact pole

recording any or all types of this particular series of leads can be derived simply by rotating the lead-selector of the switch to the indicated stations, without the necessity for interchanging any of the lead-wires attached to the electrodes on the patient. In actual use, the device has proved highly satisfactory for the purposes for which it was developed. This switch, or modified versions thereof, has also been found to provide a considerable measure of convenience when employed in practical clinical electrocardiography. Combinations of Leads I, II, and III with V leads from the six recognized precordial positions are readily recorded with its use, and the V type of unipolar limb leads are easily added to this series when desired. Moreover, this device may be regarded as a prototype, and other similar switches may be devised from it, whereby any combination of different types of leads likely to be desired for clinical or investigative purposes can be recorded with facility. Thus, the switch can be modified so that a combination of the three limb leads, the V type of multiple precordial leads, and the Goldberger type of augmented unipolar limb leads,[7] may be conveniently obtained, if such a series of leads be desired.

In publishing directions for the construction and use of this switching device, we are motivated by a desire to render presently available standard electrocardiographic equipment, of any design, suitable for the convenient recording of electrocardiograms embodying multiple types of leads, in order to promote the more general utilization and study of such multiple lead electrocardiograms. It is hoped that, in this way, a solution to the present problem of the most useful combination of multiple types of leads for ordinary purposes in practical clinical electrocardiography will be facilitated. No claim is made that the design of this device embodies other than well-known electrical principles of switch construction.

SUMMARY

A switching device is described which can be constructed easily from readily obtainable materials and which, when properly interposed in the circuit between the patient and any standard electrocardiograph, permits the rapid and convenient recording of electrocardiograms embodying multiple types of leads, without the necessity for interchanging any of the lead-wires attached to the electrodes on the patient. Experience with this device has shown that it may be used with equal serviceability for investigative studies in electrocardiography or for ordinary clinical purposes.

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Switch *C;* the wire from the left-leg terminal plug goes to Points *2* and *3* on Switch *A,* thence to Point *4* on Switch *B,* and finally through a resistor of 5,000 ohms to Point *7* on Switch *B;* the wire from the precordial (or exploring) terminal plug goes to Points *4, 5, 6,* and *7* on Switch *A.* No wires are attached to the points labelled *O* on the switch sections, since these points constitute, in the composite switch, the *OFF* station of the lead-selector.

From the common contact pole (Point *X*) of Switch *A* a wire goes to the terminal binding post located on the outside of the switch box which is labelled *G+.* The common contact poles (Points *X*) of Switches *B, C,* and *D* are wired together, and the wire from these poles goes to the terminal binding post located on the outside of the switch box which is labelled *G–.* The switch assembly framework and the sheathing of the four-wire microphone cable are connected, by wires within the switch housing, to the terminal binding post, *GND,* located on the outside of the switch box. When the switching device is in actual use, a ground wire is extended from this binding post to a suitable outside ground connection. All permanent wiring connections within the switch housing are soldered to insure good contacts.

The switching device, as described, is so constructed and wired that proper polarity of the galvanometer, according to convention,[3, 4, 10] results for each lead indicated on the switch lead-selector when the device is correctly interposed in the circuit between the patient and a standard electrocardiograph. For this purpose, the lead-wires from the switching device are connected to the proper electrodes on the patient: the "left-arm" wire from the *electrocardiograph* is attached to the switch binding post, *G+*; the "right-arm" wire from the *electrocardiograph* is attached to the switch binding post, *G–*; and the lead-selector *of the electrocardiograph itself* is constantly set as ordinarily used for taking Lead I. Once these connections and adjustments have been made, each desired type of lead is recorded after selecting the correct station on the lead-selector of the switching device. The further operation of the electrocardiograph then proceeds in the ordinary manner. For recording the different types of multiple precordial leads, each desired type of lead is chosen on the switch lead-selector, and the exploring electrode is moved manually in succession to the correct precordial position.[3, 4] For recording the unipolar limb leads of Wilson and his co-workers,[6] the lead-selector of the switching device is set to Station *V,* and the exploring electrode is moved manually to some point on the right arm, left arm, and left leg, to yield Leads VR, VL, and VF, respectively.

The composite switch, constructed as described and enclosed in a protective housing or box, may be utilized as a completely portable device, or it may be fastened to the frame of the electrocardiograph or to the supporting table, by means of angle brackets, etc. With suitable modifications in construction, the switch proper may indeed be incorporated into the electrocardiograph itself. It is important that the arrangement provide the greatest measure of convenience in actual use, since that is the essential purpose which the switching device is designed to serve.

COMMENT

The switching device described in this paper was developed in order to record with convenience, for investigative purposes, individual electrocardiograms which embody Leads I, II, III, and IVF, the CF, CL, CR, and V types of leads from precordial positions 1 to 6, inclusive, and the V type of unipolar limb leads. With this device properly interposed in the circuit between the patient and any standard electrocardiograph, the correct wiring connections for

Aschoff nodules, thickness of smooth muscle, fibrinoid degeneration, mural thrombosis, and calcific deposit; subendocardium—thickness, vascularity, cellular exudate, and Aschoff nodules.

The thickness of the endocardium proper, the subendocardium, and the smooth muscle in the outer third of endocardium was determined by means of an ocular micrometer calibrated against a stage micrometer. Each reading was made at the thickest portion of each layer. With few exceptions the borders were well defined. The outer boundary* of the subendocardium was its junction with the auricular myocardium, but adipose tissue interposed between the subendocardium and the myocardium was not included. The measurement of smooth muscle was taken in a region where the cells were compact.

The degree of vascularity of the subendocardium was estimated by counting all the vessels in this layer.

THE NORMAL LEFT ATRIUM

The term endocardium is commonly used to denote the entire inner fibromuscular elastic layer of the left atrium, extending down to the auricular myocardium. However, for descriptive purposes this layer may be subdivided into two parts, i.e., the endocardium proper and the subendocardium. The former is conveniently subdivided further into three equal zones, an inner, middle, and outer third.[4] The inner third often shows superficial regions in which the elastica is sparse or absent. The outer third usually contains compact groups of smooth muscle cells arranged parallel to the elastic lamellae. Occasionally, small transverse or longitudinal bands of smooth muscle appear in the middle or inner thirds. The subendocardium lies immediately external to the endocardium proper and consists mainly of coarse bundles of collagen; its outermost part is often loose and fibrillar and merges with the stroma of the adjacent myocardium. Sometimes, in adults, it is separated from the muscle by small amounts of fat. The endocardium proper is avascular and shows no cellular exudate. The subendocardium usually contains a small number of capillaries and may reveal a few focal collections of lymphocytes.

DESCRIPTION OF RHEUMATIC LESIONS

Widening of the endocardium proper and the subendocardium results from inflammatory lesions such as cellular exudate, increased vascularity, and fibrosis. The increase in thickness of smooth muscle in the outer portion of endocardium proper is presumably due mainly to hypertrophy. The enlarged muscle cells contain vesicular nuclei which often show variation in polarity.

The subendothelial plaque, referred to by Gross[4] as endocardial reduplication, is a papillary mass, essentially fibrous, formed by proliferation of connective tissue in the innermost part of the endocardium. A distinction was made between the typical rheumatic plaque of papillary type and the slightly elevated or flat hyaline plaque of more or less uniform width. The latter was excluded since many normal hearts show this change owing to loss of superficial elastica.

As observed in this study, there are two main types of subendothelial plaque, the hyaline and the myxomatous or mucoid. The former usually consists of a compact, sparsely cellular mass of collagen or is composed of coarse, loosely arranged bundles of collagen. The myxomatous plaque has a delicate fibrillar matrix containing cells of oval, spindle, or stellate form.

In any variety of rheumatic plaque, elastic tissue may be absent or present in slight to considerable amount. The inner margin is sometimes covered by a coarse, elastic band. Although generally composed of only one layer of connective tissue, there are plaques of so-called multiple variety which consist of two or more distinct layers separated by an elastic membrane.

*The terms "outer" and "external" indicate a location toward the epicardium; "inner" and "internal" are toward the endocardial surface.

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MICROSCOPIC LESIONS OF THE LEFT ATRIAL ENDOCARDIUM IN CHRONIC RHEUMATIC HEART DISEASE

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ENDOCARDITIS of the left atrium is a frequent and possibly constant lesion in acute rheumatic heart disease. The site of predilection is the posterior wall of the atrium, a short distance above the posterior mitral leaflet. Grossly, the endocardium is thickened, and its surface is opaque, rough, nodular, and the seat of numerous irregular ridges. Microscopically, there is usually diffuse change consisting of enlargement and hyperplasia of connective tissue cells, edema, degeneration of collagen, cellular exudate, and, in some instances, Aschoff nodules.

Most previous reports have been concerned mainly with the lesions of acute rheumatic endocarditis.[1-4] This study deals with the chronic or healed phase of the disease. The principal purpose was to determine what microscopic changes in these later lesions can be regarded as positive stigmas of rheumatic inflammation.

MATERIALS AND METHODS

Sections of the left atrium were obtained from one hundred nonrheumatic and one hundred rheumatic hearts. The rheumatic hearts were the seat of chronic or healed disease and showed no active gross lesions, i.e., verrucous endocarditis or fibrinous pericarditis. Seventy-five had mitral stenosis, and twenty-five had nondeforming mitral valvulitis. The latter consisted of thickening, opacity, and often vascularity of the valve leaflets without fusion or shortening; the chordae tendineae were also thickened. Several hearts with nondeforming mitral valvulitis showed slight aortic stenosis. Most of the hearts with mitral stenosis revealed deforming or nondeforming disease of other valves, especially the aortic and tricuspid valves. The nonrheumatic hearts were carefully selected, and those with equivocal gross rheumatic lesions rejected.

Only a single transverse section of left atrium, approximately 2.5 cm. in length, was studied. This was taken perpendicular to the endocardial surface and, according to the method of Gross, Antopol, and Sacks,[5] about 1 cm. above the attachment of the posterior mitral leaflet. There was close standardization of all sections with respect to size and location. The material was fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin. In every case an extra section was stained with the combined Weigert and van Gieson methods for elastic and connective tissue.

In addition to the nonrheumatic and rheumatic groups, sections of left atrium were also made from twenty-five hearts with syphilitic aortic insufficiency and five hearts with atypical verrucous endocarditis.

The following items were studied: endocardium proper—thickness, subendothelial plaques, fibrosis, cellular hyperplasia of connective tissue, vascularity, cellular exudate,

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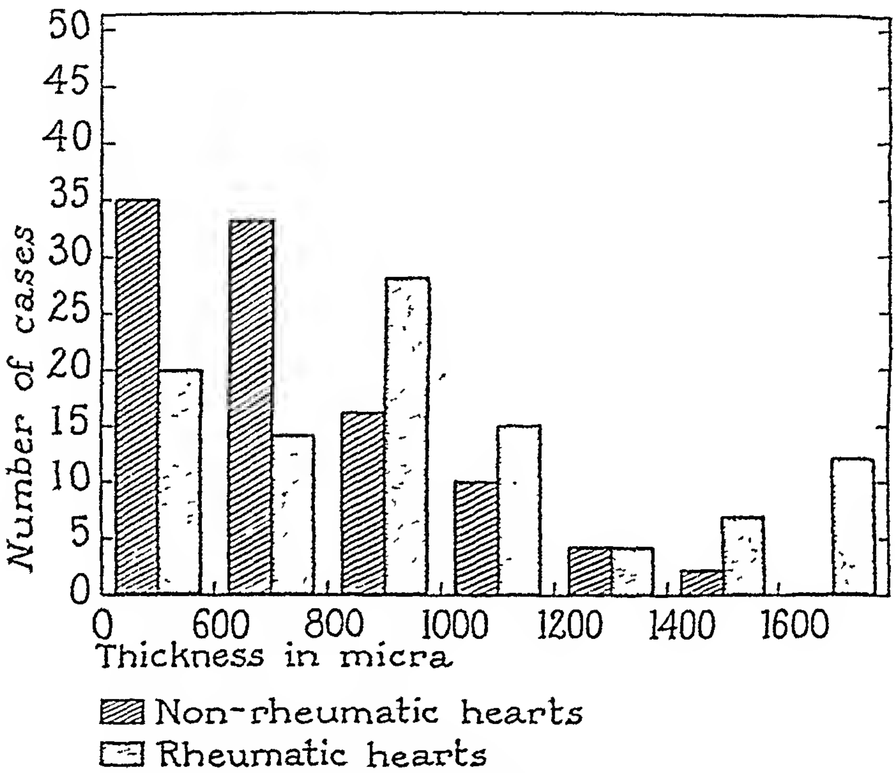
Received for publication Oct. 16, 1944.

TABLE I. LESIONS OF ENDOCARDIUM PROPER OF LEFT ATRIUM IN NONRHEUMATIC AND RHEUMATIC HEARTS

	100 NONRHEUMATIC HEARTS	100 RHEUMATIC HEARTS
Subendothelial plaque	6	23
Fibrosis	4	15
Cellular hyperplasia of connective tissue	0	18
Vascularity	2	25
Cellular exudate	0	21
Aschoff nodules	0	3
Fibrinoid degeneration	0	6
Mural thrombosis	0	5
Calcific deposit	0	1



Graph I.—Thickness of endocardium proper of left atrium in 100 nonrheumatic and 100 rheumatic hearts.

Endocardium Proper.—Thickness: In the nonrheumatic hearts the thickness of the endocardium proper varied from 330 to 1,440 microns (Graph I). The average thickness for one hundred cases was 753 microns. A value over 1,400 microns was obtained in only two hearts. The range in the rheumatic group was 330 to 3,180 microns with an average of 987. The thickness exceeded 1,400 microns in seven cases and was more than 1,600 microns in twelve cases.

Subendothelial Plaques: Plaques in subendothelial location, indistinguishable from those of rheumatic disease, were observed in six cases of the nonrheumatic group. Four were of hyaline type and two were mucoid. All plaques were of single layer variety, sparsely cellular, and contained elastic fibers, and two showed smooth muscle cells. None revealed vascularity or cellular exudate.

Subendothelial plaques were present in 23 of the 100 rheumatic hearts. In four cases there was a diffuse plaque involving almost the entire length of endocardium; in 18 cases the plaques were discrete and ranged from one to four in number per section. The plaques were of single layer type in 18 cases,

Fibrosis of the endocardium indicates proliferation of fibrous tissue or formation of scar resulting in distortion of architectural pattern and interruption of elastica. The change is focal, or patchy and diffuse, and may involve all portions of the endocardium. The fibrous lesions are often disposed obliquely or even perpendicular to the elastic lamina, are usually sparsely cellular, and sometimes accompanied by vascularity and cellular exudate.

Cellular hyperplasia of connective tissue refers to increased cellularity of endocardium and focal aggregates of mononuclear cells of histiocytic or fibroblastic type. The nuclei are vesicular or hyperchromatic, irregular in shape, often elongated, and may show palisading, while the cytoplasm is poorly defined. The polarity of the cells is variable, some being disposed obliquely, or even perpendicular, to the elastica. The intercellular collagenous matrix is sometimes the seat of swelling and degeneration.

Marked increase in vascularity of the subendocardium and vascular penetration of the endocardium proper are characteristic of rheumatic inflammation. Most of the vessels are capillaries or arterioles. A distinctive vascular lesion is observed occasionally, i.e., small arteries with thick musculoelastic wall.[4] These vessels are composed of concentric groups of longitudinal smooth muscle cells whose margins are often surrounded by elastic fibers. On cross section the artery has a honeycombed appearance.

Aschoff nodules consist of typical Aschoff cells, the Anitschkow myocytes, which have "owl-eyed," fibrocytoid, or pyknotic nuclei, distributed in an edematous matrix of swollen and coarsely granular collagen. The cytoplasm of the cells is frequently basophilic, and the cell outlines are irregular or ragged. Only nodules with typical morphology were accepted. Small groups of fibrocytes or histiocytes with normal cytoplasm and stroma were excluded.

In fibrinoid degeneration, the ground substance of connective tissue is converted to a fibrillar network or homogeneous structureless material which is poorly cellular, refractile, and intensely acidophilic.

CLINICAL DATA

All hearts were from adults. In the nonrheumatic group the ages ranged from 19 to 82 years; 52 patients were males and 48, females; 80 were white and 20, Negro. There was a variety of clinical diagnoses, such as carcinoma, pneumonia, diabetes, coronary thrombosis, and cor pulmonale. Twenty-five patients had hypertensive heart disease.

In the rheumatic group the ages varied from 22 to 78 years. There were 58 males and 42 females; 97 were white and 3, Negro. Most of the 75 patients with mitral stenosis had cardiac insufficiency of long duration with repeated attacks of decompensation and died of congestive failure. Most of the 25 nondeforming rheumatic lesions were incidental autopsy observations. None of the cases had a clinical diagnosis of active rheumatic disease.

RESULTS

A summary of the findings for nonrheumatic and rheumatic hearts is given in Tables I, II, III, IV, and V and Graphs I, II, and III. The following lesions were not observed in the nonrheumatic group: endocardium proper—subendothelial plaques with multiple layers, cellular hyperplasia of connective tissue, cellular exudate, Aschoff nodules, fibrinoid degeneration, mural thrombosis, and calcific deposit; subendocardium—small arteries with musculoelastic wall and Aschoff nodules.

Table IV. Vascularity of Subendocardium of Left Atrium in Nonrheumatic and Rheumatic Hearts

Number of vessels per section	100 nonrheumatic hearts	100 rheumatic hearts
0 to 50	97	66
50 to 74	2	6
75 to 99	0	14
100 and over	1	14

polymorphonuclear leucocytes, plasma cells, and large mononuclear cells. The exudate was confined to the outer third of endocardium in eight cases, while the middle or inner thirds were also involved in 13 additional cases. Seventeen of the 21 cases showed capillary vascularity of the endocardium and the cellular infiltration generally occurred in the vicinity of the blood vessels.

Aschoff nodules: Typical nodules, of the so-called mosaic type, were present in the endocardium of three rheumatic hearts. They were situated in the inner third of endocardium in one case, in the outer third in one case, and in both middle and outer thirds in one case.

Thickness of Smooth Muscle: In the nonrheumatic group the average thickness of the smooth muscle layer in the outer third of endocardium was 235 microns as compared to 373 microns for the rheumatic cases (Table III). The range for the nonrheumatic group was 60 to 300 microns; for the rheumatic group, 60 to 540 microns. In ten rheumatic cases the value exceeded 300 microns (Graph II).

Fibrinoid Degeneration: This occurred in six rheumatic hearts and involved connective tissue in subendothelial location or in the inner third of endocardium proper. In four instances the lesion was situated within a subendothelial fibrous plaque at the base of a mural thrombus.

Mural Thrombosis: Mural thrombi of the left atrium were present in five rheumatic hearts. They were composed mainly of fibrin and erythrocytes with a relatively small number of platelets and leucocytes. In four cases the thrombi were superimposed on subendothelial plaques.

Calcific Deposit: This was present in one rheumatic heart which showed large, coarse, calcific masses within a subendothelial plaque of dense hyaline type.

Subendocardium.—Thickness: In the nonrheumatic group, the thickness of the subendocardium varied from 90 to 480 microns (Graph III). The average was 235 microns. Ninety cases measured less than 300 microns; there were only three over 400 and none over 500 microns. In the rheumatic group the range was 90 to 900 and the average was 373 microns. Sixteen cases measured more than 400, and 20 measured more than 500 microns.

Vascularity: A count was made of all blood vessels in the subendocardium. The average area of subendocardium per section was approximately 5.9 sq. mm. for the nonrheumatic hearts and 9.3 sq. mm. for the rheumatic hearts. The total vascularity is shown in Table IV. In the nonrheumatic group the number

Table V. Cellular Exudate of Subendocardium of Left Atrium in Nonrheumatic and Rheumatic Hearts

Cellular exudate	100 nonrheumatic hearts	100 rheumatic hearts
None	75	38
Focal, slight	22	39
Focal, moderate or marked	3	4
Diffuse, moderate or marked	0	19

TABLE II. LESIONS OF SUBENDOCARDIUM OF LEFT ATRIUM IN NONRHEUMATIC AND RHEUMATIC HEARTS

	100 NONRHEUMATIC HEARTS	100 RHEUMATIC HEARTS
Vascularity (average number of vessels per section)	18	54
Musculoelastic arteries	0	6
Cellular exudate	3	22
Aschoff nodules	0	16

i.e.; dense hyaline, ten; loose hyaline, one; mucoid, four; and of both hyaline and mucoid variety, three. Plaques with two layers were present in four cases. In one instance there was a plaque with three distinct strata, a superficial mucoid superimposed upon two similar layers of dense collagen.

Elastic tissue was present in 12 and smooth muscle cells in 10 cases. Seven plaques of the single layer variety were covered superficially by a dense elastic membrane. Capillary vessels were observed in two cases, a slight cellular exudate of lymphocytes in five, and superimposed mural thrombosis in four cases.

Fibrosis: Fibrosis of the endocardium with distortion and interruption of elastica was observed in four nonrheumatic and in 15 rheumatic hearts. The lesions in each group were generally similar, except that vascularity and exudate were absent in hearts from the nonrheumatic group and present in eight of the 15 rheumatic cases.

Cellular Hyperplasia of Connective Tissue: Increased cellularity of endocardium with aggregates of swollen cells containing vesicular or hyperchromatic nuclei occurred in 18 rheumatic hearts. The collagenous matrix showed edema in 14 cases, swelling and granular degeneration in four, and cellular exudate in nine cases. Aschoff nodules were present in two cases.

Vascularity: The endocardium proper was vascularized in only two out of 100 nonrheumatic cases. In each instance a few capillaries were observed focally among smooth muscle cells in the outer third of endocardium. The middle and inner portions of endocardium were avascular in all cases.

Vascularity was present in 25 of the 100 rheumatic hearts. Most of the vessels were capillaries although two cases showed arterioles and small arteries with musculoelastic wall. The number of vessels in a single section varied from few to many and the distribution was focal or moderately diffuse. In 15 cases vascularity was confined to the outer third of the endocardium, in seven the middle third was also involved, while in three instances the capillaries penetrated into the inner third. In 15 cases the vascular change was associated with cellular exudate, usually slight and consisting mainly of lymphocytes with a few polymorphonuclear leucocytes. Focal perivascular fibrosis was present in eight cases.

Cellular Exudate: Twenty-one rheumatic cases showed this lesion which was usually focal and slight to moderate in degree. In three cases the change was diffuse and marked. The cells were mainly lymphocytes with occasional

TABLE III. AVERAGE THICKNESS, IN MICRONS, OF LAYERS OF ENDOCARDIUM OF LEFT ATRIUM IN NONRHEUMATIC AND RHEUMATIC HEARTS

	100 NONRHEUMATIC HEARTS	100 RHEUMATIC HEARTS
Endocardium proper	753	987
Smooth muscle	120	230
Subendocardium	235	373

Rheumatic stigmas of the left atrium were absent in the hearts of 25 persons with syphilitic disease, and also in the hearts of five persons with atypical verrucous endocarditis except for one case with a large subendothelial plaque.

DISCUSSION OF RESULTS

Among the nonrheumatic group were 12 hearts in which the left atrium showed one or more lesions of rheumatic type. There was a total of 18 such lesions (Tables I, II, IV, and V and Graphs I and III). To determine whether these were uncommon normal variations in structure or actually due to rheumatic disease, the 12 hearts were examined for rheumatic stigmas elsewhere than in left atrium, especially the valves. In the latter the presence of vascularity, cellular exudate, and fibrosis, especially fibroelastic reduplications of auricularis or ventricularis layers, was considered indicative of rheumatic disease.

Acceptable valvular stigmas were present in four of the 12 hearts. This leaves eight hearts not established as rheumatic with the following lesions: subendothelial plaque, four; endocardial fibrosis, three; vascularity of endocardium proper, one; thick endocardium proper, one; thick subendocardium, one; cellular exudate of subendocardium, one. Possibly these are instances of rheumatic disease with stigmas confined to the left atrium.

Some rheumatic lesions resemble and may be indistinguishable from alterations in structure of the normal atrium. This refers especially to subendothelial plaques, endocardial fibrosis, and increase in thickness of the smooth muscle. Gross[4] pointed out that, from the third decade on, thickening of smooth muscle and progressive loss of elastic tissue are commonly observed in the atrial endocardium. Loss of elastica in subendothelial location or inner third of endocardium often gives the appearance of subendothelial plaque or scar. Other rheumatic changes, such as widening of the layers of endocardium and increased vascularity and cellular exudate of subendocardium, may also be confused with normal variations. While lesions, especially if multiple, may suggest rheumatic disease, they cannot be regarded per se as characteristic unless well developed and beyond the normal range.

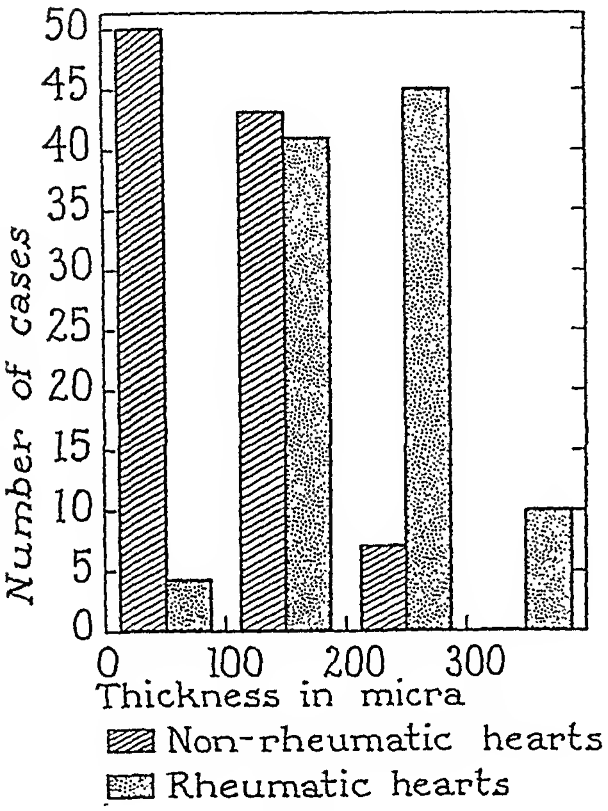
Several microscopic lesions which occur very rarely, if at all, in normal hearts or in other forms of heart disease, are practically pathognomonic of rheumatic endocarditis. The most frequent in the endocardium proper are vascular penetration, cellular exudate, and cellular hyperplasia of connective tissue; in the subendocardium the most frequent are extensive vascularity, including the presence of vessels with musculoelastic wall, and Aschoff nodules. Other changes, such as subendothelial plaques with multiple layers, fibrinoid degeneration, and calcific deposit, while conclusive, are comparatively infrequent. Gross[4] emphasized endocardial reduplications, vascularity of endocardium, and increase of endocardial smooth muscle as highly suggestive of rheumatic endocarditis in hearts with inactive disease. The atrial lesions of lupus erythematosis differ from those of rheumatic fever.[7]

Sixty rheumatic hearts showed one or more conclusive stigmas in the left atrium, while 40 were negative or equivocal. Most of the equivocal changes were probably rheumatic but not distinctive. As in the valves, rheumatic atrial disease, especially if slight, may heal without leaving diagnostic lesions.

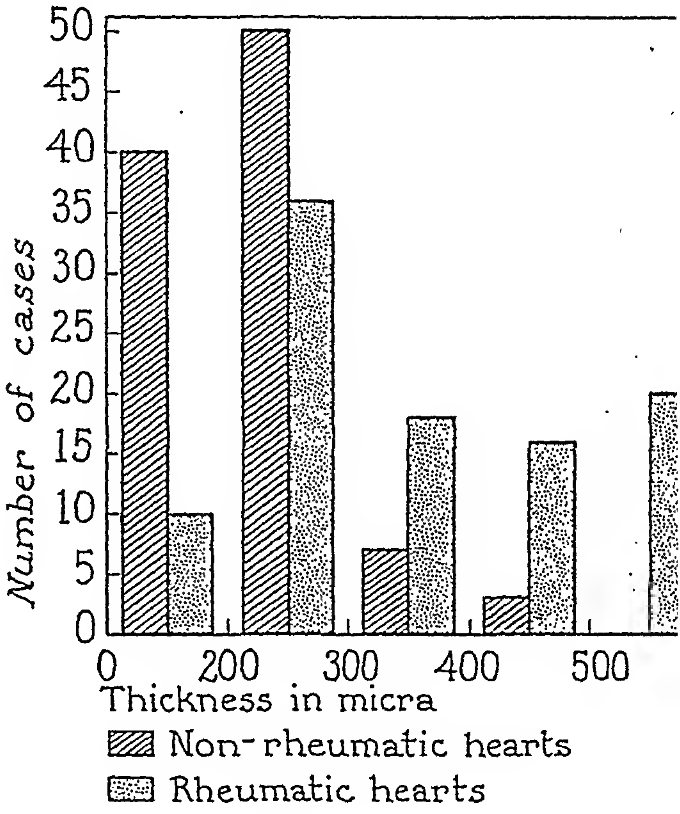
The stigmas of rheumatic disease are usually multiple. Of 60 positive hearts, 34 had three or more stigmas, eight had two, and 18 had only one. In the last group the principal lesions were Aschoff nodules, vascularity of

of blood vessels per section varied from 0 to 120 per section with an average of 18. There were less than 75 vessels in 99 cases, while one had 120. However, the last showed rheumatic valvular stigmas. No vessels with musculoelastic wall were observed. Among the rheumatic cases, the number of vessels ranged from 2 to 300 and the average was 54. More than 75 vessels were present in 14 cases and more than 100 in an additional 14. Six cases showed small arteries with thick musculoelastic wall.

The vascularity per unit area was as follows: 3.1 vessels per square millimeter of subendocardium in the nonrheumatic group and 5.8 vessels per square millimeter in the rheumatic group. The difference is statistically significant.



Graph II.



Graph III.

Graph II.—Thickness of smooth muscle layer of endocardium in 100 nonrheumatic and 100 rheumatic hearts.

Graph III.—Thickness of subendocardium of left atrium in 100 nonrheumatic and 100 rheumatic hearts.

Cellular Exudate: Of the nonrheumatic group 75 cases contained no cellular exudate in the subendocardium. Twenty-five had focal infiltration, mainly of lymphocytes and usually in the vicinity of blood vessels. This was slight and inconspicuous in 22 cases and prominent in three cases. There was no instance of diffuse exudate. In contrast, 19 rheumatic cases showed widespread exudate of moderate to marked degree (Table V).

Aschoff Nodules: Sixteen rheumatic hearts revealed subendocardial Aschoff nodules. For the size of field given previously, the number of nodules varied from 1 to 8 per section with an average of 3.3. They were usually of mosaic or reticular mosaic type with a few coronal or polaroid forms.[6] Nuclei of fibrocytoid, hyperchromatic, and "owl-eyed" type were usually present in each nodule, with the first the most frequent. The cytoplasm of the cells was frequently basophilic, and the cell margins were ragged and irregular. The connective tissue matrix showed edema and fragmentation but fibrinoid degeneration was not observed. Slight cellular infiltration was present in one or more nodules in seven cases.

erally present in acute rheumatic endocarditis. In the latter the change is diffuse and the hyperplasia of connective tissue cells is accompanied by palisading, swelling and fibrinoid degeneration of collagen, edema, and infiltration of polymorphonuclear leucocytes and lymphocytes.

Aschoff nodules are pathognomonic of rheumatic heart disease. This refers to the typical lesions and not to the so-called Aschoff-like or sub-Aschoff nodules[9] which lack precise identity. In this study the subendocardial layer of left atrium contained nodules more frequently than endocardium proper or atrial myocardium and less frequently than the myocardium of left ventricle, i.e., sixteen as compared to twenty-three cases. However, there were several hearts in which the lesion was apparently confined to the subendocardial portion of the atrium.

Fibrinoid degeneration is described as the principal change in the ground substance of connective tissue in acute rheumatic inflammation.[10] As such, the lesion was not present in this series of chronic rheumatic hearts, although a small number of cases showed fibrinoid, mainly within subendothelial fibrous plaques. The exact nature of the lesion, whether a primary degeneration of connective tissue[11-13] or due to deposition of fibrin,[14] or a combination of these,[15] is not clearly established.

Of interest is the possible relation of the rheumatic subendothelial plaque to atrial myxoma. There is a question as to whether the latter is a true neoplasm or a new growth of inflammatory type, originating in connective tissue. Dexter and Work[16] point out that a rheumatic lesion of the posterior or septal wall of the left atrium may leave a residuum on which granulation tissue develops, ultimately producing the tumor mass. In the case of myxoma which they reported, the heart showed signs of extinct rheumatic disease.

COMMENT

Stigmas of chronic rheumatic disease occur more frequently and with greater variety in the endocardial layer of the left atrium than in the myocardium or pericardium. In the latter, the only positive stigma is the Aschoff nodule; vascular lesions, fibrosis, and cellular exudate are generally not sufficient for diagnosis. Although 60 of the 100 rheumatic hearts in this study had definite stigmas in the endocardium, only five revealed positive lesions, i.e., Aschoff nodules, in the atrial myocardium.

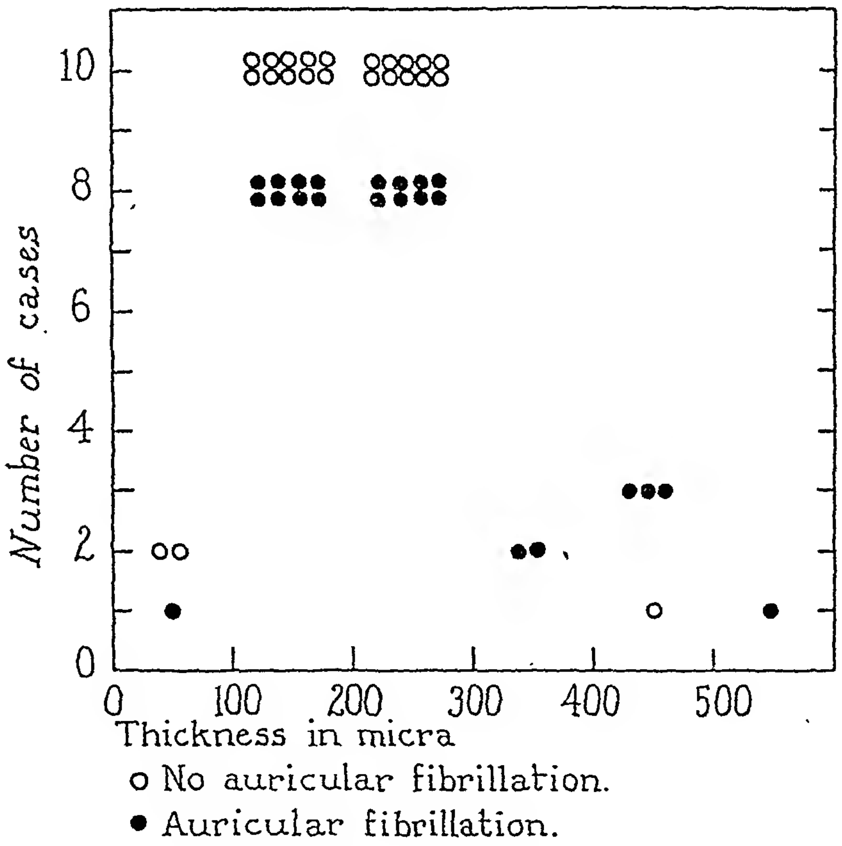
The correlation between gross and microscopic findings is shown by the following figures: of 42 hearts with gross rheumatic disease of the left atrium, 40 showed conclusive microscopic stigmas and 2 were equivocal. Of 58 hearts with doubtful gross lesion or grossly normal, 20 were positive microscopically. Thus, microscopic study may indicate rheumatic endocarditis even though the gross change is not diagnostic.

The distribution of microscopic lesions of the valves, left ventricle, and left atrium of the one hundred rheumatic hearts is shown in Table VI. The mitral valve is uniformly positive because only hearts with gross mitral lesions were selected. Stigmas of the left atrium were approximately as frequent as those of aortic and tricuspid valves and were more frequent than in pulmonary valve and left ventricle.

Hearts with well-developed, left atrial endocarditis are usually the seat of more or less widespread rheumatic involvement. All sixty hearts with atrial stigmas showed lesions in other sites, i.e.: mitral valve, 60 cases; aortic valve, 57; tricuspid valve, 42; pulmonary valve, 32; and left ventricle, 23. Three

endocardium, extensive vascularity of subendocardium, and subendothelial plaques.

In well-developed rheumatic disease there is often conspicuous thickening of the endocardial smooth muscle. Hutcheson[8] suggested that this might lead to auricular fibrillation if the smooth muscle became preponderant over the striated muscle of the atrial myocardium. Our figures in this connection are of limited value since there were electrocardiograms in only 46 cases. In 23 patients with auricular fibrillation the thickness of smooth muscle varied from 90 to 510 microns with an average of 256. For 23 patients without auricular fibrillation the range was 60 to 480 microns and the average 206. The distribution curves do not show a significant difference between the two groups (Graph IV). This was also true with respect to the thickness of atrial myocardium. In the hearts with auricular fibrillation there was no constant relation between thickness of myocardium and endocardial smooth muscle.



Graph IV.—Relation of auricular fibrillation to thickness of smooth muscle of endocardium.

Formation of new blood vessels is often a prominent feature of rheumatic atrial endocarditis. This occurs in the acute phase of the disease and the vessels remain as a stigma when activity ceases. The increase in vascularity varies from slight to marked and involves principally the subendocardium, although sometimes there is vascular penetration of the endocardium proper. While most of the new vessels are capillaries, a small number of cases show arterioles, or small arteries, with thick musculoelastic wall. The latter which are found more frequently in the valves, especially mitral, than elsewhere in the heart are especially characteristic of rheumatic disease.

Such lesions as cellular hyperplasia of connective tissue, sometimes associated with degeneration of collagen, and Aschoff nodules, indicate activity of the rheumatic inflammation. The degree and extent of cellular proliferation observed in this study were slight compared to the well-developed lesion gen-

Comparison of small groups of cases with and without auricular fibrillation showed no significant difference in the thickness of endocardial smooth muscle.

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TABLE VI. DISTRIBUTION OF MICROSCOPIC STIGMAS IN 100 CASES OF CHRONIC RHEUMATIC HEART DISEASE

	NUMBER OF CASES WITH POSITIVE STIGMAS
Mitral valve	100
Aortic valve	69
Tricuspid valve	60
Left atrium	60
Pulmonary valve	40
Left ventricle (Aschoff nodules)	26

or more of these sites were positive in 48 cases, two sites in nine cases, and only one site, the mitral valve, in four cases. Moreover, the incidence of positive stigmas in the atrium is related to the severity of the valvular disease, especially mitral. In this study, the atrium was involved in 54 of 75 hearts with mitral stenosis (72 per cent) and in only six of 25 hearts with nondeforming mitral valvulitis (24 per cent).

This limits the practical value of the atrial endocardium as a site for diagnostic stigmas of chronic rheumatic disease. When the atrium is positive there are generally clear cut valvular lesions, while in cases with slight or doubtful disease of valves the atrium is often negative. However, typical lesions of the atrium may occur in hearts with nondeforming valvulitis. Occasionally, atrial stigmas aid in establishing rheumatic disease in hearts with equivocal valvular change.

Although hearts with gross evidence of active rheumatic disease were excluded, a fairly large number—about 20 per cent—showed one or more active lesions microscopically, i.e., Aschoff nodules, cellular hyperplasia of connective tissue, and swelling and degeneration of collagen. In a few of these there was focal verrucous endocarditis of valves not recognized in gross. A clear distinction between active and acute disease is often difficult. Such lesions may indicate a recently superimposed acute rheumatic attack, or persistent activity of a previous acute attack, or possibly reactivation, especially in the stage of cardiac failure.

SUMMARY AND CONCLUSIONS

In 100 hearts, the seat of chronic rheumatic disease, there was gross involvement of the left atrial endocardium in 42 cases and microscopic involvement in 60 cases.

Certain microscopic lesions of the endocardium of the left atrium, which occur rarely, if at all, in normal hearts or in other types of cardiac disease, form practically pathognomonic stigmas of rheumatic endocarditis. In the endocardium proper these include vascular penetration, cellular exudate, and cellular hyperplasia of connective tissue; in the subendocardium they include excessive vascularity and cellular exudate, the presence of small arteries with musculoelastic wall, and Aschoff nodules.

Other lesions, such as subendothelial plaque, endocardial fibrosis, and increase in thickness of smooth muscle, may be highly suggestive of rheumatic disease but require differentiation from corresponding alterations in structure of the normal endocardium.

Rheumatic endocarditis of the left atrium usually occurs in hearts with deformity of the mitral valve and with more or less widely distributed microscopic rheumatic stigmas, especially of the valves. In occasional instances, however, atrial stigmas aid in establishing rheumatic fever as the cause of equivocal valvular disease.

first became very nervous, she was 17 years of age and was employed as a telephone operator. A diagnosis of hyperthyroidism was made, and a subtotal thyroidectomy was done. After this her nervousness disappeared for some years. But after many worries and an unhappy married life, her nervousness reappeared two years before admission. At this time she suffered a severe attack of "double pneumonia." Following this, in addition to nervousness, she began having occasional attacks of difficult breathing and coughing which occurred mostly at night. These attacks had become much more frequent and severe. At 1 A.M. the morning of admission, an especially severe attack of her "asthma" began. It was accompanied by protracted nausea and vomiting. She was referred to the Roper Hospital by her private physician.

Past history disclosed asthma in childhood which had never recurred, removal of tonsils and adenoids in childhood, appendectomy at 10 years, and salpingo-oophorectomy at 23 years. She also had had myopia since childhood requiring glasses for correction, frequent colds in the preceding two years, and menorrhagia for sixteen years. The family history was *noncontributory*.

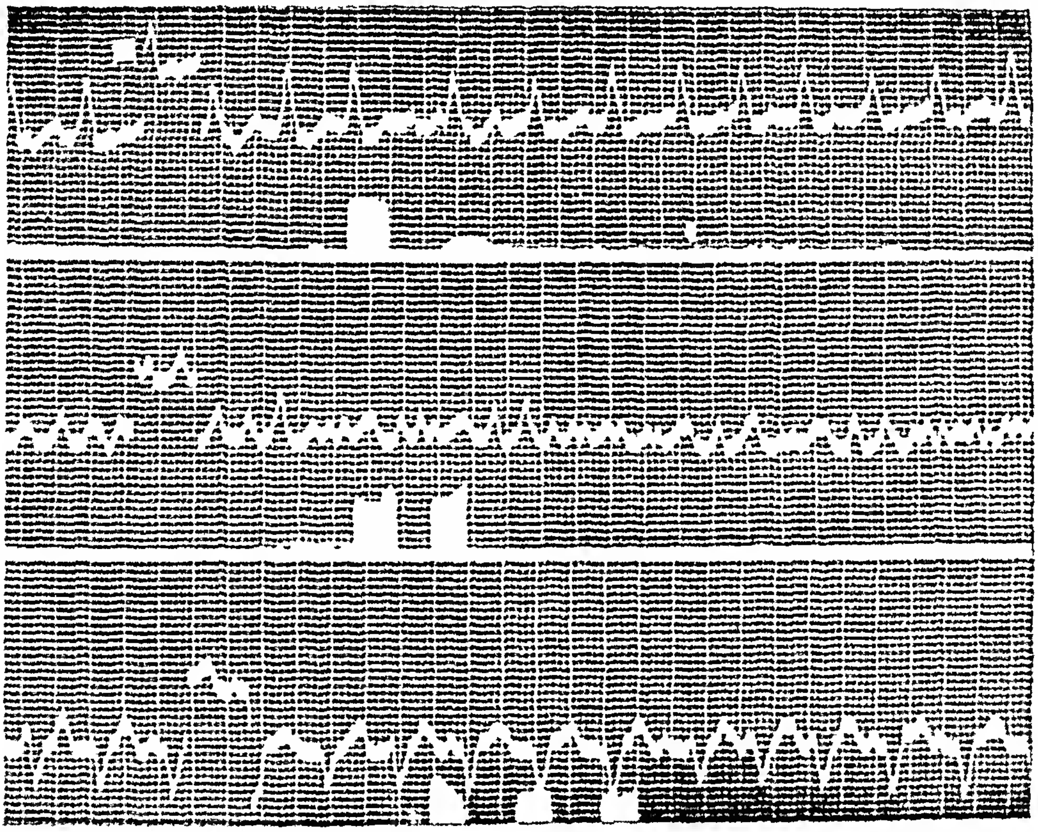

Fig. 1.

Physical examination showed a well-developed but thin, pale, nervous, and apprehensive woman of about 40 years. Her skin was fine in texture, moist, and warm. Her eyes were normal aside from myopia; there was no exophthalmos. Her tongue was rather red in color and clean, the edges were atrophic, and there was a fine tremor on protrusion. Her neck showed a scar of previous thyroidectomy. The thyroid gland was moderately enlarged, more so in the right lobe and isthmus, and was quite firm and slightly nodular. Scattered moist râles and a few musical rhonchi were heard throughout both lung fields. The heart was slightly enlarged, but there were no murmurs. The heart rate was 130 per minute, regular, but a pulse deficit of 20 was observed. The peripheral arteries were normal; the blood pressure was 150/75. The abdomen was normal except for scars of two previous operations. The extremities showed a fine tremor of the extended fingers. There was no edema. The reflexes were hyperactive.

Laboratory studies were as follows:

Urine:

Aug. 17, 1942: specific gravity, 1.020; albumin, 1 plus; sugar, 1 plus; acetone, 1 plus; and sediment, negative.

Aug. 19, 1942: specific gravity, 1.010; albumin, 1 plus; sugar, 1 plus; acetone, 0; and sediment, negative.

Clinical Reports

VENTRICULAR FIBRILLATION AS A COMPLICATION OF HYPERTHYROIDISM

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All of the authors who have described the disturbances of the heart which occur in hyperthyroidism have emphasized the fact that auricular fibrillation is the arrhythmia most commonly encountered. Transitory auricular flutter and A-V block have been noted as exceptional occurrences.[1, 2] Although the ability of thyroxin to increase the irritability of the myocardium is well known, I have been unable to find any mention in the American literature of clinical observations of arrhythmias arising from ventricular disturbances in this disease.

In Europe, Bickel[3] described two cases of sudden death in hyperthyroidism from cardiac arrest. Both patients were autopsied, but in neither was electrocardiographic proof obtained. Both deaths occurred after digitalization, and ventricular fibrillation was suggested as the cause. In Argentina, Sabathie[4] described a case of "ventricular *pre*fibrillation" in hyperthyroidism. One electrocardiogram showed auricular fibrillation, left bundle branch block, and runs of ventricular tachycardia. Another showed numerous extrasystoles from multiple ventricular foci. Five days after subtotal thyroidectomy there were found normal sinus rhythm, first degree A-V block, left bundle branch block, and occasional ventricular extrasystoles. Similar findings were obtained fourteen months later.

Bickel and Frommel[5] obtained sinus tachycardia, auricular and ventricular extrasystoles, auricular fibrillation, ventricular tachycardia, and ventricular fibrillation, all proved electrocardiographically, after massive injections of thyroid extract in rabbits. However, these results were obtained with crude extracts of thyroid glands, and all occurred within a matter of minutes after injection. Since it is well known that a latent period of twenty-four to forty-eight hours must elapse between the administration of thyroxin and the occurrence of any demonstrable biologic effect, it seems doubtful that the production of ventricular fibrillation in these experiments can be ascribed to the action of thyroxin.

Fig. 1 is an electrocardiogram obtained from a patient with recurrent hyperthyroidism. It is believed that this is the first proved instance of ventricular fibrillation in hyperthyroidism to be reported.

REPORT OF CASE

Hospital No. 11458. Mrs. L. J., a 37-year-old housewife, separated from her husband, entered the Roper Hospital Aug. 17, 1942, complaining of nervousness and asthma. When she

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Received for publication March 2, 1944.
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Sudden death in hyperthyroidism is certainly not unknown, and this was especially true in the days before Plummer's epochal discovery of the quieting effect of iodine. Moreover, a definite impression seems to have grown up among many clinicians working in large thyroid clinics that digitalis is not only ineffective, but possibly even harmful in thyrocardiac disturbances. It does not seem unreasonable to link these observations in the following conclusions.

CONCLUSIONS

1. The increased myocardial excitability in hyperthyroidism may occasionally lead to paroxysms of ventricular fibrillation.

2. Iodine is a safer and more effective drug than digitalis in controlling the arrhythmias of hyperthyroidism.

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ACUTE ISOLATED MYOCARDITIS

Report of a Case Due to Micro-Aerophylic Streptococcus Hemolyticus

John R. Schenken, M.D., and Winston C. Heibner, M.D.
New Orleans, La.

Acute isolated myocarditis or Fiedler's myocarditis is a disease which is usually characterized clinically by the sudden onset of dyspnea, cyanosis, and precordial pain, and which usually terminates fatally within a few days. In some cases, however, the onset is gradual, and, in others, the illness is protracted over a period of several months.

From a pathologic standpoint it may be defined as a "disease in which inflammation of the myocardium is the only important active acute lesion in the body"[1] and in which there is an "absence of any major pathologic condition involving either the endocardium or pericardium."[2] Anatomically it is not a specific form of myocarditis but is classified as a separate entity largely because the etiology is unknown.

The pathologic lesions in many cases of myocarditis where the etiology is known are indistinguishable from those in acute isolated myocarditis.

In a recent extensive review of the literature on isolated myocarditis, Saphir[2] stated that ". . . two distinct types of myocarditis have been described. One is characterized by the presence of granulomatous lesions and the other by

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Read before the American Society of Clinical Pathologists, June, 1943.
Received for publication March 6, 1944.

Blood:

Aug. 17, 1942: red blood cell count, 3,300,000; hemoglobin, 13 Gm.; white blood cell count, 6,700; polymorphs, 65 per cent; lymphocytes, 30 per cent; and monocytes, 5 per cent.

Aug. 18, 1942: Wassermann and Kline reactions negative. Cholesterol, 178 mg. per cent.

Aug. 27, 1942: blood sugar, 84 mg. per cent.

Significant excerpts from the progress notes were as follows: Aug. 19, 1942: Before daybreak on the morning of admission, the patient experienced a sudden attack of paroxysmal rapid heart action accompanied by an obstructive type of dyspnea and a sensation of choking in the throat. Examination showed that the lungs were clear without asthmatic wheezes. There was rapid tumultuous heart action, grossly irregular, and the rate was 150 to 160. The pulse rate, at the wrist, was 120; the pulse deficit was 30 to 40. The electrocardiogram (Fig. 1) showed auricular flutter, A-V dissociation, and intraventricular block. Lead II appears to consist entirely of a period of ventricular fibrillation. The patient stated that her "asthma" was a sensation of something pressing about her lower neck. She seemed nervous and despondent. Lugol's solution, 15 minims three times daily, was prescribed.

Aug. 20, 1942: The pulse and heart rate was 116 per minute. There was no deficit or irregularity. The patient slept well the preceding night and her nerves were calmer.

Aug. 21, 1942: The heart rate was regular; there was a systolic gallop at the apex; the rate was 100 to 120; and there was no pulse deficit. The electrocardiogram showed sinus rhythm, intraventricular block, and varying A-V block.

Aug. 25, 1942: The heart rate was regular, 100 per minute. The basal metabolism was +39 per cent.

Aug. 27, 1942: The heart rate was regular, 108 per minute. The basal metabolism was +27 per cent.

Sept. 4, 1942: Practically the whole right lobe of the thyroid was extirpated.

Oct. 24, 1942: The basal metabolism was +24 per cent.

Oct. 27, 1942: The left lobe of the thyroid was removed except for a narrow strip of normal appearing tissue behind the trachea.

Oct. 30, 1942: The patient felt very well. Her pulse was 88 per minute, her blood pressure, 140/90.

Oct. 31, 1942: The patient was discharged from the hospital.

DISCUSSION

Aside from the period of ventricular fibrillation in the tracing reproduced here, the underlying rhythm was at first assumed to be ventricular tachycardia. But a second tracing, after normal sinus rhythm was restored, showed the ventricular complexes to be of the same character as those in the first tracing, so that auricular flutter, A-V dissociation, and A-V nodal tachycardia with intraventricular conduction delay seemed to be the better interpretation. Unfortunately the technical quality of the second tracing is too poor to permit photographing for reproduction.

The present author is of the opinion that paroxysmal ventricular fibrillation may not be as unusual an event in the course of hyperthyroidism as this first case report might indicate. Since in man the diagnosis is next to impossible to make unless the patient happens to be connected to an electrocardiograph at the time the paroxysm occurs, it is possible that many instances of this arrhythmia have in the past occurred and been passed off clinically as auricular fibrillation. Such indeed was the assumption in the case presented, until the electrocardiogram unexpectedly brought to light the true nature of the arrhythmia.

Bickel[3] noted that his cases of cardiac arrest occurred after full digitalization, and felt that digitalis was contraindicated in thyrocardiac disturbances because of its effect in further increasing myocardial excitability. In this connection it should be noted that this patient received no digitalis at any time, and that the arrhythmia quickly disappeared after the administration of Lugol's solution was begun.

The heart weighed 225 grams. The chambers of the heart appeared to be moderately dilated. The endocardium was smooth and glistening, and the valves appeared normal. The myocardium was somewhat flabby. The cut surface of the left ventricle and the left ventricular side of the interventricular septum showed a zone of brownish-red muscle directly beneath the endocardium (Fig. 1). This zone, which extended from apex to base and measured 0.5 to 0.6 cm. in thickness, did not reach the endocardium at any point but remained about 0.1 to 0.2 cm. beneath it. The myocardium of the right ventricle did not show these changes. The coronary vessels were carefully inspected by serial cross sections and were widely patent throughout.

Microscopic Examination.—The lungs showed large quantities of fluid mixed with varying numbers of red blood cells in the alveolar sacs. No exudate was present. No macrophages were noted. The alveolar capillaries were dilated but there was no evidence of interstitial inflammation. The only finding in the liver was a separation of the sinusoidal walls from the liver cords. There was no evidence of chronic passive congestion. The spleen showed a moderate congestion of the pulp with an increased number of polymorphonuclear leucocytes. One Malpighian corpuscle in each section showed a central area of reticulum cell hyperplasia and necrosis. The remaining organs appeared normal.

Fig. 1.—Photograph of the left ventricle and interventricular septum of the heart. The chamber is dilated. Note the dark mottled zone beneath the endocardium.

Although the lesions in the heart were present predominantly in the mottled zone beneath the endocardium (Fig. 2), changes in the myocardium were present throughout the entire thickness of the musculature from the pericardium to the endocardium. Neither of these surfaces was inflamed. The location and the distribution of the lesions were quite irregular.

The areas showing the alteration in the muscle fibers were distributed in a patchy fashion. Some of these patches were surrounded by normal appearing muscle fibers. The changes in the muscle fibers were, for the most part, degenerative changes with the preservation of their general contour. In some areas there were irregular thickenings of the muscle fibers due to localized points of hyalinization, whereas in other areas rather long lengths of muscle fibers showed a loss of cross and longitudinal striations as the result of a rather uniform hyalinization. In both areas, however, the fibers stained more deeply than normal with eosin. In some areas the fibers showed an increase in the granularity, often revealing irregular, coarse granules and irregular, thick intercalated discs, as well as pale staining granular areas alternating with deep red staining hyalinized areas.

Inflammatory cell infiltration was associated with these degenerative changes (Fig. 3). In most areas this infiltration was rather mild, consisting largely of rows of polymorphonuclear leucocytes and a few macrophages between the muscle fibers. In other areas, however, very tiny foci of inflammatory cells were present at a point where there was obviously a defect in the continuity of the muscle fiber. None of these areas was large enough to be classified as an abscess. The densest points of accumulation of inflammatory cells were in

a more diffuse type of inflammation. . . ." It is possible that these two types may represent disease processes of different etiology, but since their separation on anatomic grounds alone is not justified they are still considered as variants of the same disease.

The vast majority of the cases which are reported in the literature has been diagnosed on the basis of the microscopic examination. The search for a causative infectious agent has been inadequate because the disease is difficult to recognize clinically and macroscopically at necropsy.

We have recently observed a case of the diffuse type of isolated myocarditis which we recognized grossly because of the rather striking macroscopic appearance. We isolated a micro-aerophylic *Streptococcus hemolyticus* in pure culture from the heart muscle.

Our review of the literature has failed to reveal any other instance where a pyogenic organism was proved to be responsible for isolated myocarditis.

REPORT OF CASE

A 16-year-old, white, American male of Jewish descent was admitted to the hospital Dec. 24, 1942, at 7:20 P.M. and died Dec. 25, 1942, at 10:20 A.M. His chief complaint was pain in the chest. On the afternoon of admission while playing basketball, the patient suddenly experienced great difficulty in breathing, saw spots before his eyes, became dizzy, and fell to the floor. He had never had any serious illnesses before, had been a regular member of the basketball team, and had been able to perform strenuous tasks without difficulty.

Physical examination revealed that the skin was cold and clammy. His blood pressure was 70/40, pulse rate 110 per minute, and temperature 98° F. He was given immediately 1,000 c.c. of 10 per cent glucose intravenously, and, following this infusion, his blood pressure rose to 90/70. Examination of the heart at this time revealed that the pulmonic second sound was louder than the aortic second sound. The mitral first sound was prolonged, but no murmurs were heard. Examination of the lungs revealed crepitant râles and a wheezing expiration. Eight hours after admission the patient was still in shock. The pulse was rapid and thready, the neck veins were distended, and the nail beds as well as the skin over the face and neck were cyanotic. He intermittently beat his chest with his hands and cried, "The pain is killing me." Coarse râles were heard over both lung bases. Just before death, which occurred about eighteen hours after the onset of illness, large amounts of pink, frothy material poured forth from the nose and mouth.

Laboratory Examination.—An x-ray film of the chest was made shortly after admission, and the following report was given: "There is a slight increase in the transverse diameter of the heart. No shift of the mediastinal structures can be detected. The vascular markings are accentuated throughout both lungs and there is a mottled clouding of the parenchyma, the impression being that of pulmonary congestion and edema. A flat plate of the abdomen reveals marked gastric dilatation." No other laboratory examinations were made.

Post-Mortem Examination.—The body was that of a well-developed and well-nourished white male, measuring 165 cm. in length and weighing 54.5 kilograms. A pinkish-white froth filled the nasal and oral cavities. The superficial veins of the neck were markedly distended. The skin of the face and neck, the mucous membranes, and the nail beds were deeply cyanotic. There was no edema of the extremities or the back.

The peritoneal cavity contained about 40 c.c., each thoracic cavity contained 500 c.c., and the pericardial sac contained about 30 c.c. of a clear, straw-colored fluid. No exudate was present upon the serous membranes.

The right lung weighed 620 grams and the left, 460 grams. Each lung showed similar findings. Pinkish-white froth filled the large bronchi, and clear fluid poured forth from the cut surface. There was no evidence of consolidation. The liver weighed 1,212 grams. The capsule was smooth, the margins sharp, and the cut surface revealed normal color and markings. The gall bladder and bile ducts were normal. The spleen weighed 150 grams, and its capsule was smooth. The cut surface was irregular and deep purple in color; the pulp was softer than normal, but the markings were preserved. The right kidney weighed 112 grams, and the left, 125 grams. A moderate degree of congestion was the only finding of note. The pancreas, suprarenal glands, urinary bladder, gastrointestinal tract, and testes appeared normal.

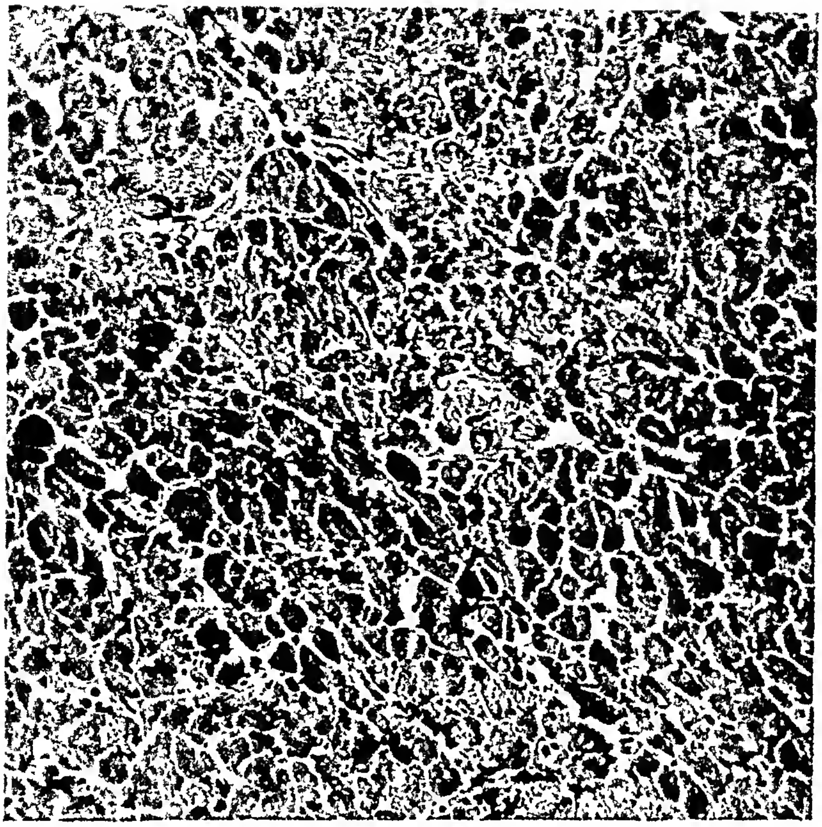

Fig. 4.—Photomicrograph of the myocardium. Early degenerative changes without inflammatory cell infiltration. The fibers in the central portion stain more deeply and the striations are obscure (hematoxylin and eosin stain; magnification, ×230).

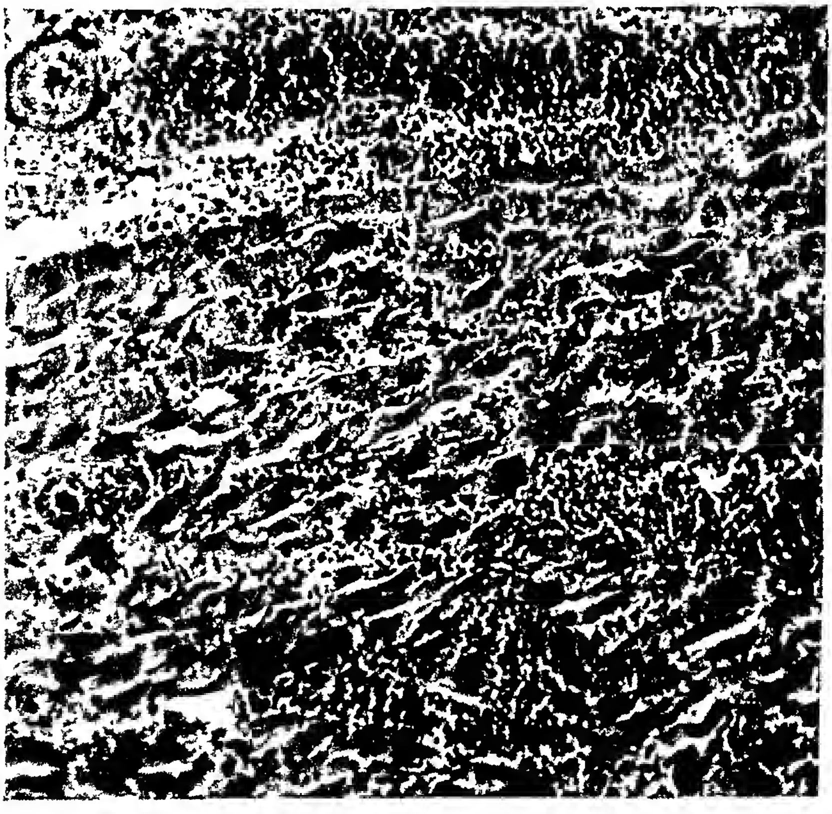

Fig. 5.—Photomicrograph of the myocardium. Note the hemorrhage between the muscle bundles and in the perivascular tissues. Degeneration of the muscle fibers is indicated by the loss of striations, granularity, thickened intercalated discs, and fragmentation (hematoxylin and eosin stain; magnification, ×230).

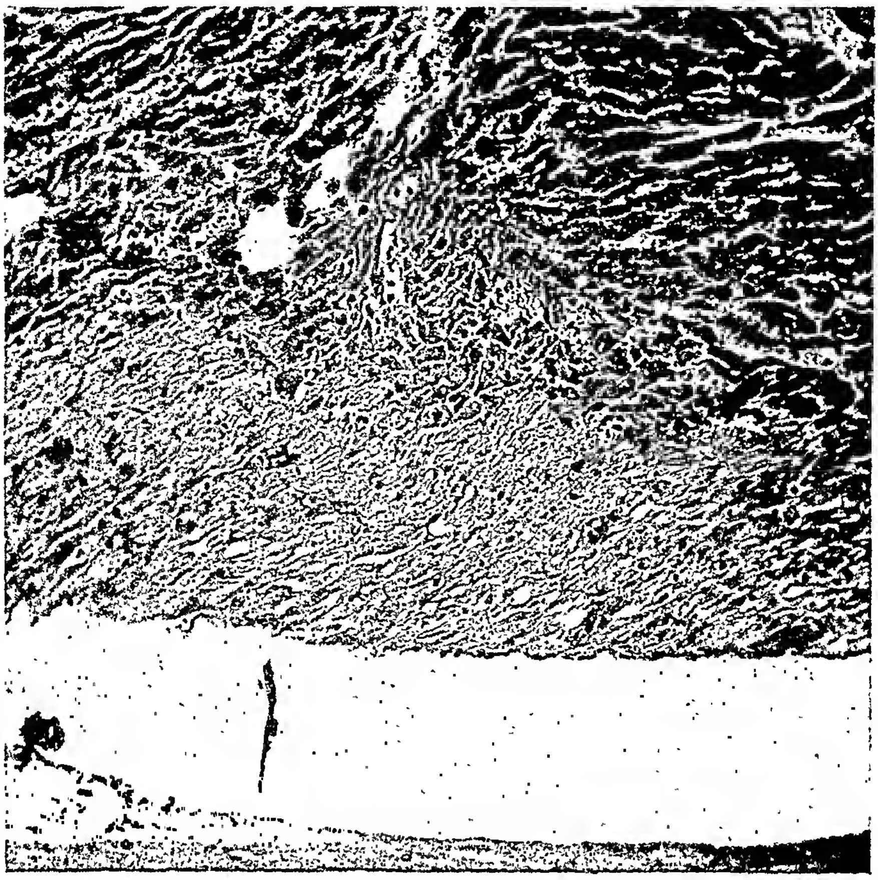

Fig. 2.—Photomicrograph of the myocardium showing the zone of unaffected muscle fibers directly beneath the endocardium. The fibers undergoing degeneration stain deeply with eosin and the striations are obscure (hematoxylin and eosin stain; magnification, ×120).

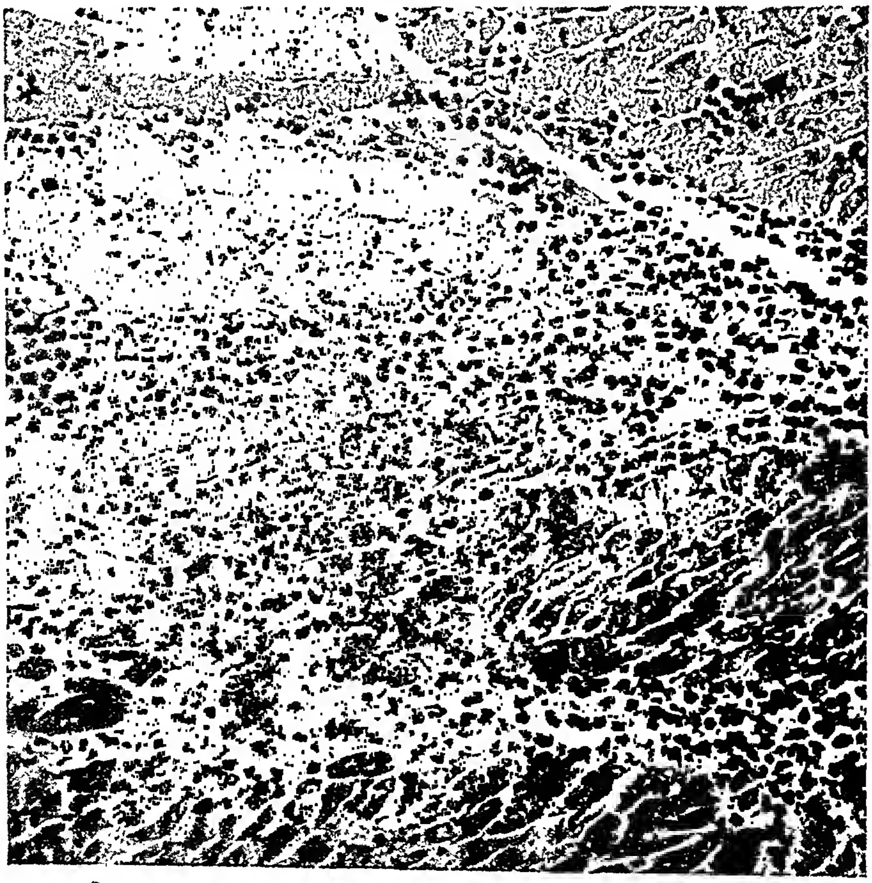

Fig. 3.—Photomicrograph of the myocardium. The muscle fibers are necrotic and the area infiltrated with polymorphonuclear leucocytes (hematoxylin and eosin stain; magnification, ×230).

Abstracts and Reviews

Selected Abstracts

Mazer, M., and Reisinger, J. A.: An Electrocardiographic Study of Cardiac Aging Based on Records at Rest and After Exercise. Ann. Int. Med. 21: 645, 1944.

The present study demonstrates but few significant differences between the electrocardiographs of males in the third and fifth decades. In tracings taken at rest, significant differences between the two age groups were found only in the frequency of Q waves in Lead III, the voltage of R waves in the limb leads, and the voltage of T waves in Leads I and II.

It has been found also that, though the alterations in the QRS complex due to exercise show definite average trends, there are individual variations in either direction. Hence, definite criteria for the normal variation of this component cannot be established. The changes after exercise in the S-T segment were more constant and the variations from the average were small. Except for the T wave in Lead I in one case, all of the T waves in Leads I, II, and IV were upright after exercise. Low voltage of the T waves in all of the limb leads or in the chest lead was not seen after exercise.

From the data of the present study the following criteria for an abnormal electrocardiographic response to standard exercise in the age groups considered are suggested:

1. Depression of the S-T segment (by exercise) of more than 0.75 mm. in Lead I, 1.5 mm. in Lead II, 0.75 mm. in Lead III, and 1.75 mm. in Lead CF_4.
2. Inversion of the T waves in Leads I, II, or CF_4.
3. Low voltage of the T waves in all of the limb leads.

McCulloch.

Kreutzer, R.: Further Experience in the Surgical Treatment of Persistence of the Ductus Arteriosus. Rev. argent. de cardiol. 11: 240, 1944.

Four observations of ligation of the ductus arteriosus are presented. In two cases the results were optimal though some cardiovascular anomalies persisted. The murmurs disappeared. A third patient died four days after operation. No autopsy was made, but, from the clinical and radiological symptoms, death may be imputed to pulmonary atelectasia and purulent pleuropericarditis. In the fourth case the murmur which disappeared after ligation reappeared eight months later with the same characteristics, though less intense.

The author's observations are in line with Shapiro's opinion that operation should be performed only when the cases of persistent ductus arteriosus, not accompanied by other cardiac malformations, show signs of heart enlargement or insufficiency or, in their absence, of bacterial endocarditis.

Author.

Gilchrist, A. R.: Patent Ductus Arteriosus and Its Surgical Treatment. Brit. Heart J. 7: 1, 1945.

Patency of the ductus arteriosus has been studied in a series of twenty-eight consecutive patients, fourteen of whom were submitted to surgical ligation.

In diagnosis, emphasis is placed on the almost pathognomonic sign—the continuous murmur of Gibson. In the absence of the characteristic murmur, the diagnosis can still be established by the detection of other signs which, taken together, are of almost equal value. In order of importance these are: pulmonary artery dilatation, increased pulse pressure at rest or after exercise, and a long harsh basal systolic murmur with an accentuated or reduplicated pulmonary second sound.

The defect is in the nature of an arteriovenous fistula. In patent ductus arteriosus the ventricular outputs are unequal, the left exceeding the right by the amount of flow through the ductus. This in turn is regulated, at least in part, by the size of the channel and the degree of resistance offered by the peripheral arterioles of the pulmonary circuit, the constriction of which decreases the burden thrown on the left ventricle by correcting the tendency to an excessive fall in diastolic pressure.

the relatively loose supporting tissue in the region of the large blood vessels. In some areas there was hyalinization of the muscle fibers associated with very little cellular infiltration (Fig. 4). In general, however, the degree of cellular infiltration was dependent upon the severity of the degenerative process. In many areas, marked hemorrhage was associated with degeneration and rupture of the muscle fibers (Fig. 5). There was no evidence of pre-existing disease.

Bacteriologic Studies.—No ante-mortem bacteriologic studies were made. Blood taken from the heart at autopsy was inoculated into brain broth, and no bacterial growth occurred. The splenic pulp was cultured on brain broth and was sterile. A block of myocardium, measuring about 1 sq. cm., was placed in acetone for one minute in order to destroy the contaminating surface organisms. It was then transferred to a sterile mortar and triturated with sterile sand and broth. Portions of this material were then inoculated into brain broth, Brewer's fluid thioglycollate medium, and upon a blood agar plate. A pure culture of microaerophylic *Streptococcus hemolyticus* was isolated. No contaminating organisms appeared in any of the media.

DISCUSSION

The various etiological agents which have been suggested as the cause of isolated myocarditis include the *Treponema pallidum,*[3] bacteria and bacterial toxins of an unknown type,[1, 2] a virus,[4] and *Staphylococcus citreus.*[5] Syphilis is admittedly responsible for a number of cases of myocarditis, but is certainly not the cause of the majority of cases of isolated myocarditis. None of the other agents have been proved to be responsible for the disease.

Among the cases reported in the literature, organisms were searched for in three cases. In the case reported by Rindfleisch,[5] *Staphylococcus citreus* was isolated from the myocardium. Abscesses were not found in the heart muscle, and hence its etiological relationship remains in doubt. In the other two cases reported by Scott and Saphir,[6] organisms were searched for by staining the tissue and not by culture. It is questionable whether this method of examination would reveal the presence of small numbers of organisms. Using a Gram's method which stains organisms very well in control tissues, we were unable to find organisms in the myocardium in our case.

The lesions in the myocardium are not unlike those which are caused by known infectious agents where the myocarditis is not the sole active inflammatory lesion.

In this case we know that the micro-aerophylic *Streptococcus hemolyticus* was the causative agent. It is hoped that the myocardium will be cultured in other instances. This procedure may reveal that isolated myocarditis is more commonly caused by an infectious agent than is now appreciated.

SUMMARY

1. A case of diffuse type of acute isolated myocarditis is reported.

2. A micro-aerophylic *Streptococcus hemolyticus* was isolated in pure culture from the myocardium. Cultures of the blood and spleen remained sterile.

3. Many cases of acute isolated myocarditis are probably due to an infectious agent, but the failure to recognize the condition clinically or grossly at necropsy has prevented proper bacteriologic studies.

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Some murmurs may be perceived at the olecranon even when a cuff on the arm is inflated to a pressure higher than the systolic pressure of a patient. The intense murmurs of pulmonary stenosis, of an intraventricular communication, and of aortic stenosis or insufficiency may be transmitted to the elbow or to the carotid arteries: this fact proves that murmurs are not transmitted by the blood stream but propagate in all directions from their origin and are specially well conducted by bone.

The present teachings on the propagation of murmurs should be revised, and, in general, the study of the nature of murmurs requires more research. AUTHOR.

Peeples, G. S. T.: The Rheumatic Fever Program in South Carolina. J. South Carolina M. A. 40: 205, 1944.

A brief description is given of the Rheumatic Fever Program under the provisions of the Service for Crippled Children of the Children's Bureaus Service. This program is one of those conducted in about nineteen states at the present time. The details will be of interest to those who are conducting similar programs or who are interested in their initiation.

MCCULLOCH.

Lange, K., and Boyd, L. J.: The Functional Pathology of Experimental Frostbite and the Prevention of Subsequent Gangrene. Surg., Gynec. & Obst. 80: 346, 1945.

The tissue alterations after exposure to severe cold are described, and the sequence of events as well as the vascular occlusion due to stasis is discussed. The sequence of functional changes after exposure to mild cold, as elicited by the fluorescein test, is described, and emphasis is placed upon the arteriolar spasm and decreased capillary permeability. These vascular changes are independent of central nervous system influences and seem to occur by axon reflexes.

Cold sufficient to solidify the exposed tissues causes a complete interruption of circulation during the exposure. This is always followed by a period of complete restoration of circulation and increased capillary permeability as evidenced by the fluorescein test. This period lasts for six to sixteen hours after exposure. This is the most promising period for therapeutic endeavors. The period of circulatory restoration is followed by one with arteriolar and capillary occlusion resulting from the formation of red blood cell clots. Gangrene of the associated area is the consequence. Heparin administered during the period of circulatory restoration prevented gangrene in sixteen rabbits whereas all controls had complete gangrene of the part. Five animals were exposed by freezing small areas; in the remaining animals the entire hind leg was frozen. Although tissue loss was averted by the early use of heparin, sensory and motor nerve paralysis was often not prevented.

Fourteen cases of human frostbite show that the fluorescein test permits the exact prediction of subsequent superficial tissue loss provided certain precautions are taken. Great surgical conservatism is in order in frostbite since these lesions show a marked tendency to heal. Moreover, the rules for amputation in occlusive vascular disease are not applicable in frostbite. After an injection of fluorescein the dye content of the blisters seems to afford a good insight into the vascular damage in the deeper structures. AUTHORS.

Woodbury, R. A., and Abreu, B. E.: Influence of Dying Gasps, Yawns and Sighs on Blood Pressure and Blood Flow. Am. J. Physiol. 142: 721, 1944.

Gross and *net*, left and right ventricular pressures are recorded from dogs without operative entrance into the chest by means of hollow sounds inserted down the left carotid into the left ventricle and down the right jugular into the right ventricle.

Normal inspiration increases venous return to the right heart and produces contour changes characteristic of larger and more prolonged effective ejection without significantly changing the duration of systole.

Dying gasps, deep breathing, yawns, and sighs, which are generally considered as respiratory acts, markedly increase venous return. In the presence of cardiac arrest, dying gasps pump blood through the lungs and temporarily provide blood flow to the vital areas, the central nervous system, and the heart. Effective *net* pressure as great as 50 mm. Hg in the pulmonary artery, 50 mm. Hg in the coronary arteries, and 10 mm. Hg in the central nervous system arteries was created by dying gasps in dogs where cardiac action had ceased.

AUTHORS.

Most cases are observed in childhood, and 70 per cent are detected before the age of 20 years is reached. After this, the condition becomes increasingly rare. The scanty number of adults so affected can be explained on several grounds, such as death in youth, spontaneous closure of the ductus in childhood, or on the failure of the clinician and pathologist to look for this lesion systematically in older patients.

Of fourteen patients (Cases 15 to 28) in whom surgery was judged unnecessary or undesirable, the eldest was 49 and the youngest 5 years, with an average age of 20 years. Two died, one from intercurrent infection and one from subacute bacterial endarteritis. Slight deterioration in physical capacity was observed in three patients. Two women married and have borne families without undue distress. In one patient, a 6-year-old boy, the ductus closed spontaneously.

Of the fourteen patients submitted to surgery, distinct improvement in the general health and physical capacity was observed in six. Four obtained less benefit than anticipated, chiefly because complete obliteration of the ductus was not always obtained. Two patients died in the period after operation.

The diagnosis of the infected ductus is discussed. As an aid to its recognition, emphasis is placed on the value of repeated x-ray examinations. The radiological appearances are, on occasions, unique. The changing pattern of the heart and lungs makes a sequence so characteristic that the diagnosis of bacterial endarteritis of the ductus and pulmonary artery should seldom be missed.

Two patients submitted to surgery on account of bacterial endarteritis died. Death in each instance was attributed to massive pulmonary collapse.

Problems of the postoperative period are discussed. The occurrence of respiratory complications, recanalization of the ductus after ligation, the significance of a return of the Gibson murmur after operation, and the course of the blood pressure response are considered.

The selection of patients for surgery demands careful consideration. The main factors to bear in mind are the age of the patient and the degree of cardiac embarrassment. In general, the younger patient should be accepted for surgery when symptoms are minimal, in the hope that by ductal occlusion the child may grow and develop normally. In older patients, on account of the increasing operative hazards, surgery can be justified only when symptoms, being more severe, warrant the risk. In the presence of an infected ductus, ligation should be undertaken without delay at any age. AUTHOR.

Luisada, A. A., and Wolff, L.: The Significance of the Pulmonary Diastolic Murmur in Cases of Mitral Stenosis. Am. J. M. Sc. 209: 204, 1945.

Three cases of mitral stenosis, two with associated interauricular septal defect, are described in which pulmonic insufficiency was constantly present and independent of congestive failure. None have died. Phonocardiographic records of the murmurs are included.

The clinical signs of pulmonary insufficiency and its differentiation from aortic insufficiency are reviewed from the literature and tabulated. Pulmonary insufficiency is not always transient and functional in cases of mitral stenosis with or without interauricular septal defect, but may be permanent and organic as in the cases here reported. The nature of the possible organic changes is discussed.

AUTHORS.

Levine, S. A.: Certain Observations Referring to Cardiac Murmurs and to Their Mode of Transmission. Arch. Inst. Cardiol. Mex. 14: 150, 1945.

The speed of the blood in the cardiac cavities and in the large vessels is an important factor in the production of murmurs and in determining their intensity. It is responsible for the appearance of presystolic murmurs under similar conditions in cases of incipient mitral stenosis. The same factor is responsible for the systolic murmurs that occur in conditions such as anemia, hyperthyroidism, and fever.

In clinical explorations it is useful to grade the intensity of murmurs. For this purpose, one may designate as grade 1 the weakest murmurs, with grade 6 the strongest (those perceptible with the stethoscope at a short distance from the thoracic wall), and one may assign to murmurs of intermediate intensity the grades 2 to 5. Systolic murmurs of grade 3 or higher denote usually some organic disease or some other pathologic condition. Systolic murmurs of grade 1 and sometimes those of grade 2 are often present in healthy subjects. Weak murmurs may disappear during deep inspiration even when caused by cardiac disease.

The rate of decline in heart size lessened after the first quarter of the postoperative survival and later the heart size did not change or even increased slightly. It is suggested that these later changes may be due, in part at least, to the development of myocardial ischemia as a result of the slowed rate of blood flow, shared by the coronary circuit, leading to a loss of cardiac tone.

AUTHORS.

Kleinberg, W., Swingle, W. W., and Hays, H. W.: Intramuscular Pressure Changes in Shock. Am. J. Physiol. 143: 89, 1945.

Henderson's method was utilized for studying changes in intramuscular pressure under the following experimental conditions: (a) pentobarbital sodium anesthesia of long and short duration; (b) before and after intravenous injection of adrenalin; (c) following morphine plus pentobarbital sodium anesthesia; (d) fatal shock induced by four different procedures; and (e) sublethal hemorrhage without shock.

Pentobarbital sodium anesthesia of twelve hours' duration did not induce any greater change in intramuscular pressure than anesthesia lasting two to three hours. Adrenalin, administered by vein, raised both the blood pressure and intramuscular pressure, but the latter remained elevated long after the blood pressure had returned to normal. Morphine, followed by intravenously administered pentobarbital sodium, lowered both the arterial pressure and intramuscular pressure for several hours. Shock induced in deeply anesthetized dogs by (a) release of limb tourniquets; (b) application of a limb press; (c) trauma to muscle masses of the hind legs; and (d) gunshot injury was accompanied in all cases by marked fall in the intramuscular pressure. Sublethal hemorrhage, without shock representing 33 c.c. per kilogram of body weight, caused a sharp rise in intramuscular pressure which was maintained for several hours after spontaneous return of the blood pressure to normal. Reinfusion of heparinized whole blood in the hemorrhaged dogs resulted in decline of the intramuscular pressure to control levels.

AUTHORS.

Canzanelli, A., Guild, R., and Rapport, D.: Tourniquet Shock in the Rabbit. Am. J. Physiol. 143: 97, 1945.

Shock was produced in the rabbit by occlusion of the circulation in the hind legs. After two hours of occlusion at room temperature, the survival time after tourniquet release was 3.8 = 0.6 hours; after five hours of occlusion it was 1.7 = 0.4 hour. Thus a technique with predictable results is offered for the study of shock. Tourniquet shock in the rabbit is not due to loss of fluid in the ligated legs. Chilling the tourniqueted legs more than tripled the average survival time in most experiments; in the remainder death was delayed as much as twenty-four hours. Dehydration and previous fasting did not affect the survival time.

AUTHORS.

Wiggers, H. C., Ingraham, R. C., and Dille, J.: Hemorrhagic-Hypotension Shock in Locally Anesthetized Dogs. Am. J. Physiol. 143: 126, 1945.

Combined moderate and drastic hemorrhagic-hypotension of the intensity recommended for production of irreversible shock in anesthetized dogs induces this condition even more regularly in locally anesthetized dogs. Specifically, mortality was 100 per cent in our Series A dogs, even though only two of the thirteen dogs were permitted to endure the full 135-minute hypotension period. Under these conditions (a) postreinfusion survival times were shorter; (b) equivalent or smaller bleeding volumes were required to establish hypotension of equal intensity, and (c) the pathologic findings at autopsy were more extensive and intense than in a series of barbitalized dogs previously studied under these conditions. The conclusion was reached that (a) the barbitalized dog is equally if not better equipped to withstand the rigors of this procedure; (b) barbital anesthesia, per se, neither facilitates nor fosters the onset of shock when administered properly, and (c) a simplified and less severe shock producing procedure is desirable if a large series of shock experiments in locally anesthetized dogs is contemplated. It is suggested that psychic, emotional, or other neurogenic factors which frequently prevail under local

Altschule, M. D., Iglauer, A., and Zamcheck, N.: Respiration and Circulation in Patients With Obstruction of the Superior Vena Cava. Cerebral Factors in Dyspnea and Orthopnea. Arch. Int. Med. 75: 24, 1945.

A study of the respiratory and cardiovascular dynamics in five patients with obstruction of the superior vena cava revealed that hyperventilation, with a consequent fall in alveolar carbon dioxide, often occurs in this syndrome. Stasis may be present in the brain of a patient with obstruction of the superior vena cava. High venous pressure and slowed circulation time do not necessarily indicate the presence of stasis. Studies of the blood gases are more helpful in this regard.

It is concluded that the occurrence of hyperventilation, dyspnea, orthopnea, or periodic breathing in a patient with obstruction of the superior vena cava is associated with tissue stasis in the brain.

AUTHORS.

Frank, H. A., Altschule, M.D., and Zamcheck, N.: Traumatic Shock. IX. Pressor Therapy: The Effect of Paredrine on the Circulation in Hemorrhagic Shock in Dogs. J. Clin. Investigation 24: 54, 1945.

Vasoconstriction is not maximal in hemorrhagic shock in the dog; arterial and venous pressures can be raised for considerable periods of time by paredrine. The responsiveness to paredrine diminishes or is lost late in shock or after repeated dosage. The increase in arterial and venous pressures is not accompanied by an improvement in blood flow. The increase in alertness and activity following effective paredrine injection in shock is not explained. These experiments do not indicate whether the vasoconstrictor effect of paredrine during hemorrhagic shock exerts a useful or harmful effect.

AUTHORS.

Mylon, E., Cashman, C. W., Jr., and Winternitz, M. C.: The Relation of Adrenalin and of the Carotid Sinus to the Hyperglycemia of Shock. Am. J. Physiol. 142: 638, 1944.

Hyperglycemia after hemorrhage varies in extent with the rate of blood loss. It can be prevented by quantitative replacement with Tyrode solution immediately after each blood withdrawal. The anoxia attained is independent of blood loss or of replacement with Tyrode solution and cannot be the cause of the elevated blood sugar. Carotid sinus or vertebral artery ligation does not influence hyperglycemia after hemorrhage. Adrenalin hyperglycemia is mild as compared with that of hemorrhage. Carotid sinus or vertebral artery ligation abolishes or minimizes the hyperglycemic response to adrenalin even when there is adequate liver glycogen as demonstrated by chemical assay or by response to bleeding. The dependence of adrenalin hyperglycemia upon this neural mechanism suggests that the lack of the hyperglycemic response to adrenalin after hypophysectomy may be a result of damage to this pathway rather than to absence of the gland. Insulin sensitivity also is increased after carotid sinus or vertebral artery ligation, but not to the extent that follows hypophysectomy. It may result from interference with adrenalin activity essential both for the restoration of blood sugar and for the decrease of the excitability of the central nervous system.

AUTHORS.

Kondo, B., and Katz, L. N.: Heart Size in Shock Produced by Venous Occlusion of the Hind Limbs of the Dog. Am. J. Physiol. 143: 77, 1945.

Changes in heart size following the production of shock by bilateral venous occlusion of the hind limbs of the dog were studied by means of x-ray. X-ray films of the heart in the anteroposterior and left lateral positions were taken, retraced, and the shadow area determined by planimetry. In some experiments, heart rate was controlled by atropinization.

Control studies showed that a change of heart size of 5 per cent, if uniform and consistent, was probably significant, and a 10 per cent change was unequivocal.

The operative procedure employed led to a consistent decline in heart size greatest in the first hour. This decline was attributed to the loss of circulating blood volume as shock developed, the rate of loss lessening as the experiment progressed.

Guerra, F.: Biometric Studies Concerning Digitalin. Arch. Inst. Cardiol. Mex. 14: 160, 1945.

The generic term, digitalin, includes digitalic substances which differ qualitatively and quantitatively. In view of their chemical complexity their metabolism in the organism differs, hence the discrepancies in the clinical activity of the several crystalline digitalins. The main objection to the method of intravenous perfusion in the cat (adopted by the Committee of Hygiene of the League of Nations, by the U.S.P. XII, and by the other pharmacopoeias) is that, although this method is acceptable for the preparations made out of *Digitalis purpurea* and *Digitalis thapsi*, it is not adequate for those derived from *Digitalis lanata*, for which it is necessary to consider the gastrovenous coefficient. Furthermore, the biologic response obtained with the standard of powdered leaves of digitalis is qualitatively and quantitatively different from that obtained with pure glucosides or with the so-called digitalins.

The statistical instability of the *cat unit* indicates the need of a reference standard for the digitalins which should be effective clinically when administered by different routes and should be sufficiently stable for accurate control. With the purpose of finding such a standard, five samples of pure digitalins were titrated: Digitalin (A and B) powder, American process; Digitalin (C) crystallized by the French process; Digitoxin (D), identified by some with the crystalline Digitaline of Nativelle; and Digitalinum (E) powder, German process. The method followed was that of the U.S.P. XII, using two groups of six cats for each sample and adjusting the technical details to those of the international collaborative assay of the standard of digitalis leaves.

As a basis for future discussion of an international standard for digitalin, special care was taken to develop the study in terms of the statistical theory of all-or-nothing reactions, which has been established precisely on digitalis by the speculations of Trevan, de Lind van Wijngaarden, Gaddum, and Fisher, and especially those of Bliss, based on calculations of maximum likelihood.

For each sample the following are described: cumulative frequency, use of probits and of logarithmic doses for the transformation of the curve into a straight line, standard deviations, variation coefficients, and tests of skewness and of kurtosis. A later analysis of variance discusses the variation within and between the several samples titrated, their error, and the consistency and homogeneity of the results. The relative potency of the samples studied is established using, as a comparative standard, the titration of the sample of digitalin D (digitoxin), because of its stability both from the technical and from the clinical standpoint.

AUTHOR.

Book Reviews

NEFROPATIA GRAVIDICA: By Dr. José Reynaldo Marcondes, University of São Paulo, Brazil. São Paulo, 1944, 191 pages.

This monograph is based upon 80 observations on 79 cases, including 45 toxemias of pregnancy and 35 other hypertensive and renal syndromes.

Toxemia of pregnancy is considered as due to an endocrine unbalance caused by a placentogenic substance. This would cause diffuse angiospasm, with secondary renal ischemia. Whenever the latter persists too long, irreversible renal lesions occur.

The monograph fails to present any new data of interest, but is nevertheless a careful and complete study of the subject. Differential diagnosis and treatment are discussed in detail.

ALDO LUISADA.

anesthesia as employed may partially account for the apparently greater susceptibility to the standardized hemorrhagic procedures observed in these experiments.

A less severe and less time consuming procedure was used in thirteen dogs (Series B) and was found more satisfactory. Irreversible shock was achieved in only 77 per cent of the animals; the others survived indefinitely. However, it is believed that shock can be attained in every instance by modifying the duration of the hypotension period. It appears that severe irreversible changes seldom develop until at least sixty minutes of hypotension (40 to 45 mm. Hg) have been endured.

In most of the nonsurviving dogs, a specific reaction was recognized which indicated that irreversible shock had been produced and that further continuance of the low arterial blood pressure period was unnecessary. Thus, once the blood pressure shows a persistent tendency to decline from the established hypotensive level, even immediate reinfusion of all withdrawn blood does not prevent eventual death from shock. It is considered doubtful that any remedial measures at present proposed for hemorrhagic conditions can do more than prolong the onset of death, once this reaction occurs.

Their dogs were at all times responsive to their environment, even in the advanced stage of hypotension. They never approached the moribund or comatose state until the terminal moments of the postreinfusion period as cardiorespiratory failure approached. Vomiting and/or bloody diarrhea were common occurrences in these dogs. This is mentioned inasmuch as Moon did not observe these phenomena in the uncomplicated hemorrhagic experiments he performed. Obviously, they are not distinctive features of shock dogs as differentiated from hemorrhaged dogs as Moon asserts.

The subjection of dogs, locally anesthetized, to an abbreviated (sixty minute) period of hypotension (40 to 45 mm. Hg) before reinfusion of all withdrawn blood will not induce shock in most instances; nine of ten dogs survived this procedure. By reinfusing various blood or plasma substitutes instead of the blood withdrawn, their relative efficiency in severe hemorrhagic conditions can be evacuated.

AUTHORS.

Walcott, W. W.: Blood Volume in Experimental Hemorrhagic Shock. Am. J. Physiol. 143: 247, 1945.

Blood volume studies were carried out on twenty-three unanesthetized dogs in hemorrhagic shock produced by a single rapid bleeding. Determinations were made of the magnitude of the compensatory reserves involved in the early restoration of the blood volume. These reserves averaged 10.7 per cent of the control blood volume but ranged from 3 to 18 per cent. It was concluded that for dogs under these conditions the blood volume must be reduced by at least 40 per cent to lead to progressive fatal shock.

AUTHOR.

Walcott, W. W.: Standardization of Experimental Hemorrhagic Shock. Am. J. Physiol. 143: 254, 1945.

A method is prescuted for the standardization of hemorrhagic shock in the unanesthetized dog. The method consists of the rapid determination of the bleeding volume followed immediately by infusion of 25 per cent of the blood collected. This procedure requires less than ten minutes. A fixed volume of 10 ml. is subsequently withdrawn at half-hour intervals. This method of bleeding invariably produces fatal hemorrhagic shock. In a series of thirty dogs on which this method was employed the survival time averaged three hours, forty-five minutes.

AUTHOR.

Scherer, J. H., and Howe, J. S.: Fatal Cardiac Tamponade Following Sternal Puncture. J. Lab. & Clin. Med. 30: 453, 1945.

The second death from sternal puncture recorded in the literature and the first autopsy on such a case is reported. The cause of death was cardiac tamponade, due to hemorrhage from laceration of the right ventricle by the needle.

AUTHORS.

American Heart Association, Inc.

1790 Broadway at 58th Street, New York, N. Y.

The American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty eminent physicians who represent every portion of the country.

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HEART DISEASE: By Paul Dudley White, M.D., Lecturer in Medicine, Harvard Medical School, and Physician to the Massachusetts General Hospital, Boston. The Macmillan Co., New York, 1944, ed. 3, 976 pages plus index, 138 illustrations, $9.00.

The revision of this book is based on additions made during the six years since the previous edition. Its value is obviously enhanced by the additional clinical experiences of the author and the clinical judgment that comes from years of study and careful observations.

The more important additions and revisions pertain to the range of the normal heart, phonocardiography, precordial leads, ligation of the patent ductus arteriosus, present status of the treatment of subacute bacterial endocarditis, splanchnic resection for hypertension, intracardiac thrombosis, pulmonary thrombosis, and other vascular accidents. The results are in keeping with the high standards maintained in the past. The addition concerning the range of the normal heart is particularly deserving of mention, especially at present because of the help that it may afford in the determination of the fitness of young men for military service. As pointed out by the author, this subject has been grossly neglected in the past and thus is deserving of more attention in the future. The extensive bibliography continues to be one of the excellent features of the book.

This book is well known to the profession through the past editions and because of the prominent position long held by the author in this field. Thus a recommendation is not needed, but merely an announcement that a new edition is available.

FRED M. SMITH.

BLOQUEIOS DE RAMO EM CLÍNICA: By A. B. Benchimol, Assistente da Faculdade Nacional de Medicina, Rio de Janeiro. Livraria Atheneu, Rio de Janeiro, 1943, 149 pages, 83 illustrations.

This work is based upon a very extensive survey of the literature and on the study of forty cases of bundle branch block. The evolution of ideas on bundle branch block is followed through ample quotations and also by reproducing the original tracings of different authors from Lewis (1916) to the latest contributions.

After a chapter on diagnosis and classification, the author studies different types of bundle branch block by means of electrocardiography and other graphic methods. Special attention is given to precordial leads. Unstable, focal, and bilateral block and the Wolff-Parkinson-White syndrome are discussed in detail.

In the following chapter, modifications caused by myocardial infarction on electrocardiograms of bundle branch block are reviewed, and the influence of both ventricular hypertrophy and the position of the heart is discussed. In spite of the difficulties presented by the association of bundle branch block with the two above-mentioned conditions, diagnosis is possible. The clinical study is illustrated by electrocardiograms and phonocardiograms.

There is still a divergence of opinion on the interpretation of bundle branch block tracings, according to Benchimol, but multiple precordial leads help in doubtful cases. The view that most of the electrocardiographic changes thought to be characteristic of bundle branch block are void of any meaning is justly supported by the author; he accepts only prolongation of QRS as evidence of the lesion.

The importance of other graphic methods (phonocardiography, sphygmography, and phlebography) in revealing asynchronous contraction of the two ventricles is properly emphasized. Evidence of delayed contraction of one ventricle represents, after all, absolute proof of the existence of bundle branch block.

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Printed in the
United States of America

Press of
The C. V. Mosby Company
St. Louis

AMERICAN HEART JOURNAL

For the Study of the CIRCULATION

©Am. Ht. Assn.

PUBLISHED MONTHLY
Under the Editorial Direction of
THE AMERICAN HEART ASSOCIATION

VOLUME 29
JANUARY—JUNE, 1945

ST. LOUIS
THE C. V. MOSBY COMPANY
1945

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